U

Uranium(VI) Fluoride[1]

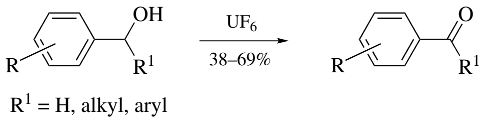
UF_6

[7783-81-5] F_6U (MW 352.03)
InChI = 1/6FH.U/h6*1H;/q;;;;;;+6/p-6
InChIKey = SANRKQGLYCLAFE-CYFPFDDLAO

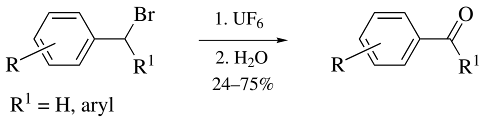
(strong oxidant;[1] fluorinating agent;[2] mild Lewis acid[3])

Physical Data: mp 64.8 °C; sublimes at 56.5 °C; vapor pressure at room temperature 115 mmHg.[4]
Solubility: sol Freon, chloroform, methylene chloride.
Form Supplied in: white crystalline compound. Available in the ^{235}U depleted form as a byproduct of uranium enrichment plants.
Handling, Storage, and Precautions: UF_6, depleted of fissionable ^{235}U, contains less than 0.20% ^{235}U. It is corrosive, moisture sensitive, and mildly radioactive (low level of radiation). Caution should be exercised against these potential hazards. UF_6 is best handled in all copper apparatus. However, Freon solutions of UF_6 are stable and do not attack glass. This reagent should only be handled in a fume hood.

Oxidation. UF_6 is a strong oxidant. Its oxidizing ability compared with that of other higher fluorides of f- and d-elements in Groups 5 and 6 is in the following sequence: $VF_5 > UF_6 > MoF_6 > WF_6 > MoF_5$.[1] Another study shows that, in acetonitrile, UF_6 is a stronger oxidant than MoF_6, NO^+, and Cu^{2+}.[5] UF_6 reacts with higher alkanes, alkenes, and arenes vigorously to give carbonaceous substances; this is of little synthetic value.[1] However, it has been used to oxidize partially oxidized organic compounds selectively. UF_6 reacts with benzylic alcohols and bromides readily to form aldehydes or ketones in moderate to good yields (eqs 1 and 2).[2] Oxidation of alkyl bromides or iodides is, however, not successful.

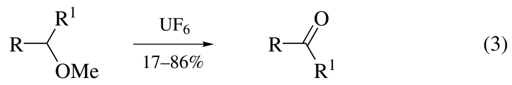


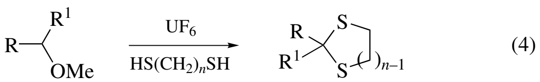
R^1 = H, alkyl, aryl



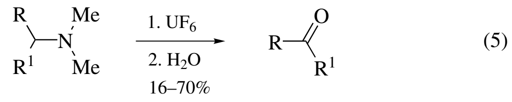
R^1 = H, aryl

Alkyl methyl ethers are oxidatively cleaved to the corresponding carbonyl compounds (eq 3). When alkyl benzyl and alkyl benzhydryl ethers are used in the reaction, the parent alkyl alcohols are obtained together with benzaldehyde and benzophenone, respectively.[2] UF_6 is also effective in cleaving allyl ethers, but the direction of the cleavage is unpredictable. The intermediates of the oxidation can be intercepted by dithiols to form dithioacetals (eq 4). Tertiary amines (*N,N*-dimethylamines) react similarly with UF_6 to yield the corresponding carbonyl compounds (eq 5).

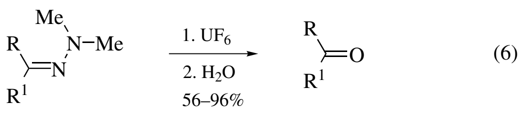


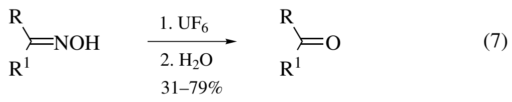


n = 2, 3

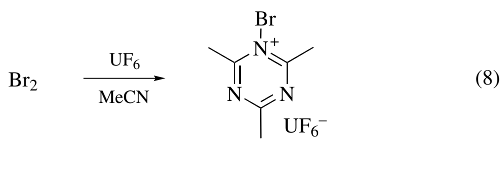


Hydrazones and oximes react with UF_6 to regenerate the parent carbonyl functions (eqs 6 and 7).[2] This offers a new alternative for these deprotections.





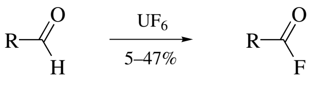
Oxidation of iodine by UF_6 in acetonitrile yields bis(acetonitrile)iodine(I) hexafluorouranate(V).[6a] In the case of bromine, oxidation generates tris(acetonitrile)bromine(I) hexafluorouranate(V) with a possible 1,3,5-triazine like structure (eq 8); this can be further utilized to brominate arenes.[6b]



Fluorination. Aliphatic alcohols react with UF_6 in the gas phase to form fluoroalkanes, alkenes, and ethers.[7] For primary alcohols, fluoroalkanes are the major products (eq 9). This is a valuable reaction, since it is difficult to prepare primary fluorides, especially methyl fluoride.

$$RCH_2OH \xrightarrow[\text{gas phase}\ 18\text{–}99\%]{UF_6} RCH_2F \qquad (9)$$

Both alkyl and aryl aldehydes have been converted to acyl fluorides in moderate yields (eq 10).[2] Adamantanone is oxidatively fluorinated to 2,2-difluoroadamantane in 41% yield (eq 11).[2] On the other hand, UF_6 behaves as a mild Lewis acid towards enolizable ketones, leading to their condensation.[8] UF_6 reacts with carboxylic acids to form acyl fluorides,[1] but in some cases this reaction is accompanied by decarboxylation.[9]



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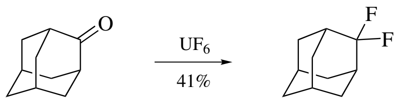

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1. Orekhov, V. T., *Russ. Chem. Rev. (Engl. Transl.)* **1977**, *46*, 420.
2. (a) Olah, G. A.; Welch, J., *J. Am. Chem. Soc.* **1978**, *100*, 5396. (b) Olah, G. A.; Welch, J.; Ho, T. L., *J. Am. Chem. Soc.* **1976**, *98*, 6717.
3. Olah, G. A. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: New York, 1963; Vol. 1.
4. Oliver, G. D.; Milton, H. T.; Grisard, J. W., *J. Am. Chem. Soc.* **1953**, *75*, 2827.
5. Anderson, G. M.; Iqbal, J.; Sharp, D. W. A.; Winfield, J. M.; Cameron, J. H.; McLeod, A. G., *J. Fluorine Chem.* **1984**, *24*, 303.
6. (a) Anderson, G. M.; Winfield, J. M., *J. Chem. Soc., Dalton Trans.* **1986**, 337. (b) McGhee, L.; Rycroft, D. S.; Winfield, J. M., *J. Fluorine Chem.* **1987**, *36*, 351.
7. Schnautz, N. G.; Venter, P., *S. Afr. J. Chem.* **1992**, *45*, 59.
8. Goosen, A.; McCleland, C. W.; Venter, P. J.; Venter, M. W., *S. Afr. J. Chem.* **1987**, *40*, 30.
9. Nguyen-Nghi, H.; Chuong, P. P. V.; Beaucourt, J. P.; Lellouche, J. P.; Sergent, L., *Ann. Chim. Fr.* **1984**, *9*, 709.

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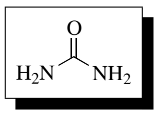
Urea[1]



[57-13-6] CH_4N_2O (MW 60.07)
InChI = 1/CH4N2O/c2-1(3)4/h(H4,2,3,4)
InChIKey = XSQUKJJJFZCRTK-UHFFFAOYAF

(nitrogen nucleophile; carbonyl cation equivalent; formation of inclusion complexes is used to purify long, slender compounds)

Physical Data: mp 132.7–132.9 °C; *d* 1.335 g cm^{-3}.
Solubility: sol H_2O (108 g/100 mL at 20 °C), EtOH (5.4 g/100 mL at 20 °C), MeOH (22 g/100 mL at 20 °C).
Form Supplied in: colorless solid.
Purification: reagent graded commercial products are sufficiently pure for most purposes. For further purification, see Perrin and Armarego.[2]

Original Commentary

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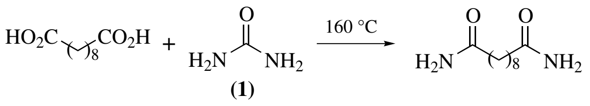
Nitrogen Nucleophile. The three heteroatoms of urea, i.e. two nitrogens and an oxygen, are moderately nucleophilic. A number of highly regioselective alkylation reactions of urea have been developed. In most cases, the nitrogen atom is alkylated to afford the corresponding ureides or amino compounds. On heating a mixture of a carboxylic acid and urea (**1**) at around 160 °C, the corresponding amide is obtained (eq 1).[3,4] In the presence of ***Triphenyl Phosphite*** and ***Pyridine***, aromatic carboxylic acids react with urea at lower temperatures to give the corresponding arylcarbonylureas in good yields (eq 2).[5]



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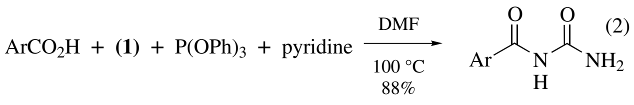
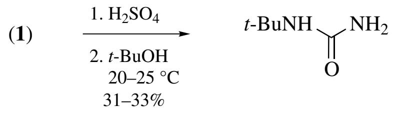


(2)

Urea serves as a nitrogen nucleophile toward tertiary carbocationic species to give *N*-*t*-alkylureas;[6,7] for example, the *t*-butyl cation, generated by treatment of *t*-BuOH with H_2SO_4, is trapped with urea to give *t*-$BuNHCONH_2$, a useful precursor of ***tert-Butylamine*** (eqs 3 and 4).[6]



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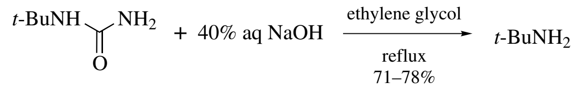
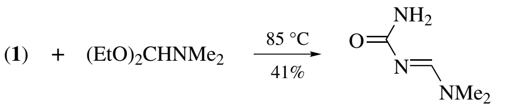


(4)

Urea reacts with orthoesters and related compounds to form alkylideneurea derivatives. The reaction with ***N,N-Dimethylformamide Diethyl Acetal*** gives *N*-carbamoyl-*N′*,*N′*-dimethylamidine (eq 5).[8] Active methylene compounds may further participate in the condensation reaction of ***Triethyl Orthoformate*** and urea to form ureidomethylene derivatives (eq 6).[9] Treatment of urea with ***Chlorine*** in the presence of ***Calcium Carbonate*** provides monochlorourea, which may be utilized as a source of ***Hypochlorous Acid*** (eq 7).[10,11]



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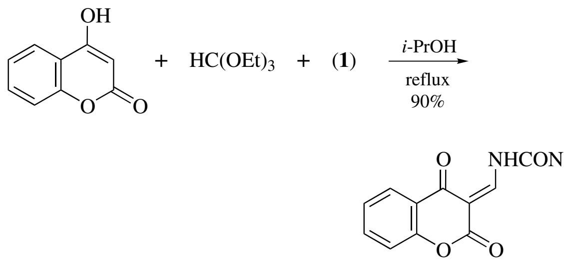

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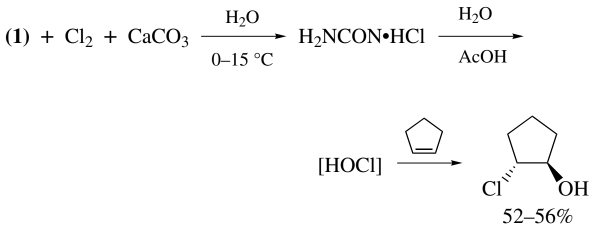
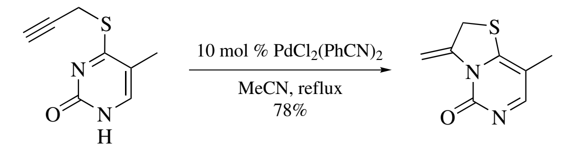


(7)

Under mild conditions, urea undergoes nucleophilic addition to carbon–carbon triple bonds (eq 8)**[12]** and double bonds (eq 9)**[13]** activated by the coordination of Pd^{II} species. Under 1 atm of ***Carbon Monoxide***, intramolecular aminocarbonylation proceeds at 0 °C to room temperature to provide protected *β*-amino acids (eq 9).**[13]**



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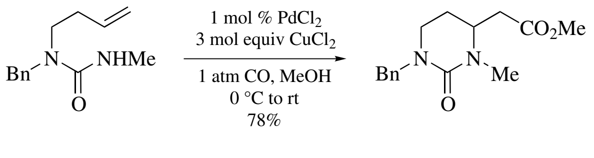
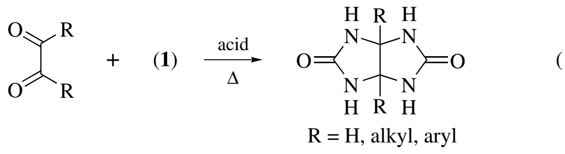


(9)

Two of the three heteronucleophilic centers of urea react with difunctionalized carbonyl compounds (e.g. dicarbonyl compounds, *α*-halo- or *α*-hydroxy carbonyl compounds, and *α*,*β*-unsaturated carbonyl compounds) to furnish a wide range of nitrogen heterocycles. The dicarbonyl compounds include ***Glyoxal***, *α*-diketones (eqs 10 and 11),**[14–16]** *α*-keto esters (eq 12),**[17]** oxalic and malonic esters (eq 13),**[18,19]** *β*-diketones (eq 14),**[20]** and *β*-keto esters (eq 15).**[21]** A three component connection reaction of urea, aldehydes, and *β*-keto esters provides dihydropyrimidines (Biginelli reaction) (eq 16).**[22]**



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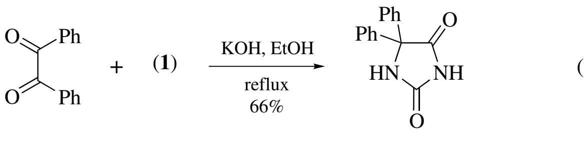

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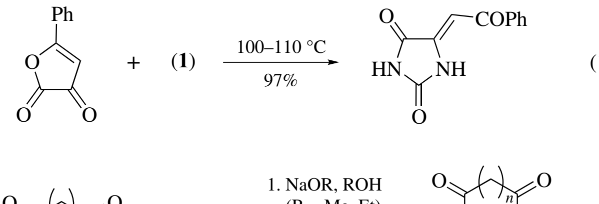

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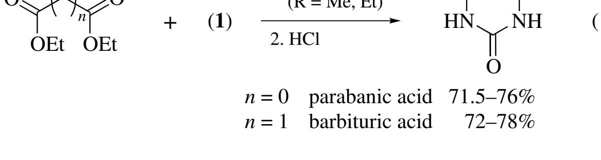

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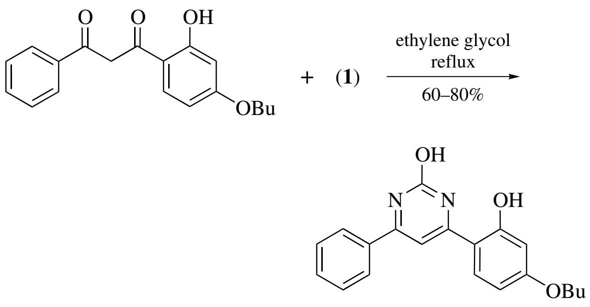

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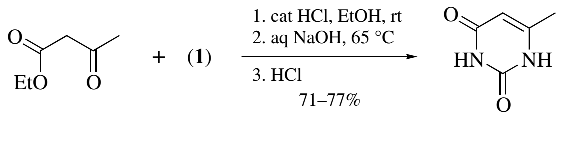

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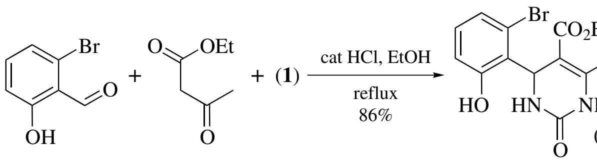
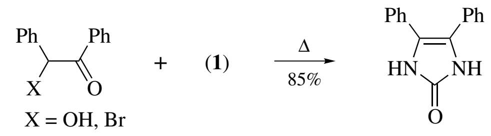


(16)

The reaction of urea and carbonyl compounds with *α*-substituents, such as *α*-hydroxy ketones**[23]** and *α*-halo ketones,**[11]** may afford either imidazol-2-one derivatives (eq 17) or oxazole derivatives (eq 18).**[24]** The latter is a rare example of the *N,O*-dialkylation of urea.



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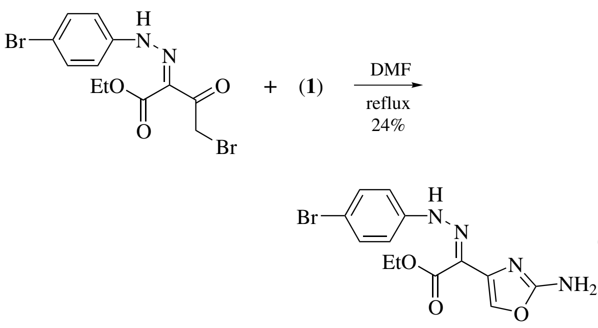
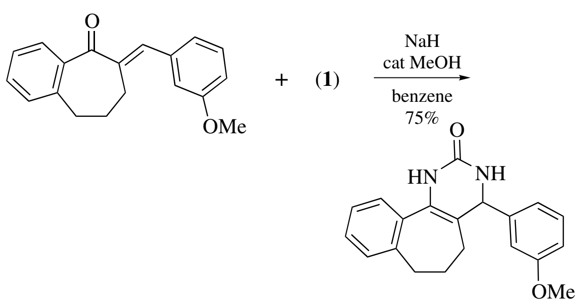


(18)

α,*β*-Unsaturated ketones and acids react with urea to give dihydropyrimidine derivatives (eq 19)**[25]** and dihydrouracils (eq 20),**[26]** respectively. *α*,*β*-Unsaturated aldehydes and ketones with *β*-substituents, such as alkoxy,**[27]** amino,**[28]** halogeno,**[29]** trichloromethyl,**[30]** etc.,**[31]** provide substituted pyrimidines (eq 21).



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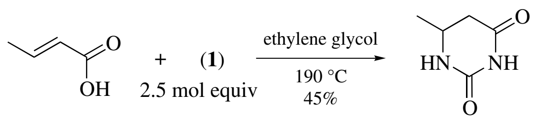

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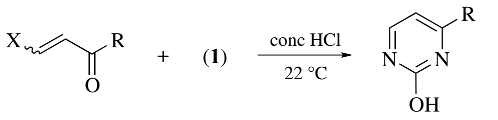
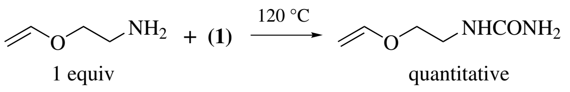


(21)

X = OEt, NMe_2, Cl, CCl_3, etc
R = H, alkyl, aryl

Carbonyl Cation Equivalent. In the reaction with heteronucleophiles, urea acts as a carbonyl cation or dication equivalent, like phosgene and carbonates, though requiring more drastic conditions. *N*-Substituted or *N,N′*-disubstituted ureas can be prepared by transamination of the urea nitrogen atoms with primary amines (eqs 22 and 23).[32] Reaction of urea with *vic*-diamines (eq 24)[33] and 2-aminophenols (eq 25)[34] gives imidazolidin-2-ones and oxazolidin-2-ones, respectively. The reaction with aliphatic 2-amino alcohols, on the other hand, gives imidazolidin-2-ones via substitution by the hydroxyl group for a nitrogen of urea (eq 26).[35,36] The *cis*-1,5-dimethyl-4-phenylimidazolidin-2-ones, obtained by fusing (−)- or (+)-ephedrine hydrochloride and urea, are useful chiral auxiliaries for asymmetric syntheses.[36]



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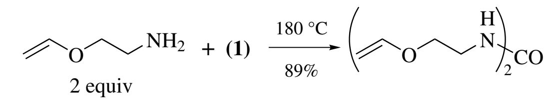

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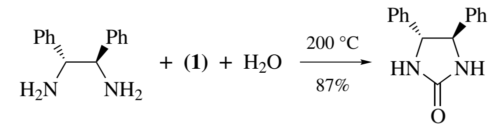

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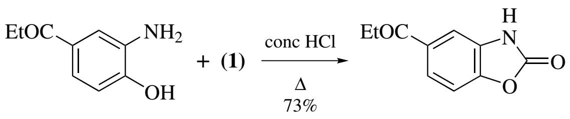

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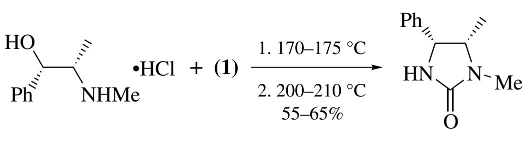
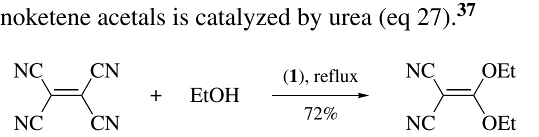


(26)

Catalyst. The conversion of ***Tetracyanoethylene*** into dicyanoketene acetals is catalyzed by urea (eq 27).[37]



(27)

Inclusion Compounds (Differentiation of Linear Compounds from Branched Ones).[1,38] Urea forms inclusion complexes, taking normal alkanes having six or more carbon atoms as guests.[39] In the complexes, hydrogen bonded urea molecules are oriented in a helical lattice, constructing a cylinder-shaped channel. The guest molecule is not bonded to the host but merely trapped in the cylinder. The diameter of the channel is usually about 5.25 Å. Aliphatic hydrocarbons with a single methyl branch, such as 3-methylhexadecane, that form the complex require a channel diameter of about 5.5 Å. This seems the upper limit of thickness. Not only hydrocarbons but many kinds of functionalized alkanes can be included if they are long and slender enough. Compounds that form inclusion complexes include 1-bromohexane, 1- and 2-octanol, 2-heptanone, 1-cyclopentylnonane, and 2-, 3-, and 4- methyltridecane. On the other hand, the following compounds do not form the complex: 3-ethyldodecane, 2-bromooctane, 1-cyclohexyloctane, and 2,4-dimethyldodecane.[40] Thus linear compounds, as in the former group, can be separated from a mixture with small or branched ones such as in the latter. *syn*-9,10-Dihydroxystearic acid has been separated from its *anti* counterpart.[41] The *syn*-diol (mp 95 °C), which is estimated to require a channel diameter of 5.4 Å, readily forms a urea complex. On the other hand, the *anti*-diol (mp 131 °C), which requires a channel diameter of 6 Å, does not form a complex.[38]

First Update

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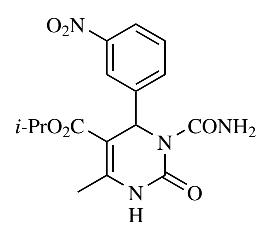
Array BioPharma, Boulder, CO, USA

Nitrogen Nucleophile. The Biginelli reaction, an acid-catalyzed cyclocondensation reaction between a β-keto ester, an aldehyde, and urea, is used to prepare dihydropyrimidinones (eq 16).[22] There has been a remarkable amount of attention given to this transformation due to the interesting pharmacological properties associated with dihydropyrimidinones.[42] Many biologically active molecules including calcium channel modulators, anticancer compounds, and α_{1a} adrenoreceptor-selective antagonists contain the dihydropyrimidinone scaffold. Some examples are illustrated below.



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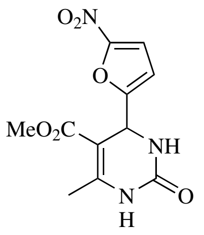
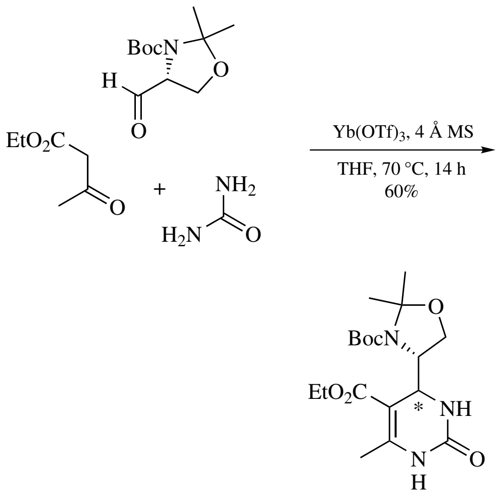


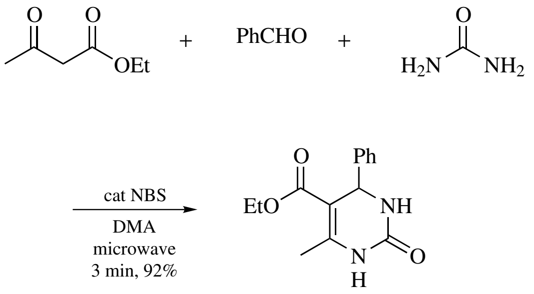
Nitractin

A wide variety of modifications to this reaction include the use of many different Lewis acids,[43] microwave conditions,[44] solvent-free green conditions,[45] and reactions performed using solid support for parallel synthesis (eqs 28–30).[46] The cited references are a few examples; a comprehensive list of these reactions is beyond the scope of this article. There are a number of excellent reviews detailing the scope of the Biginelli reaction.[47] In a related application of this reaction, the tethered Biginelli condensation is used in the preparation of biologically active guanidine alkaloids.[48]

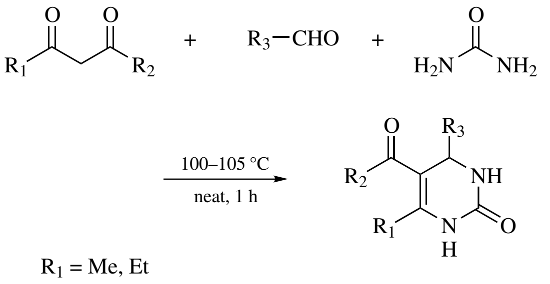


(28)

4*R*/4*S* = 5:1



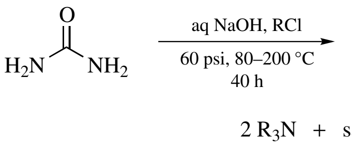
(29)



(30)

R_1 = Me, Et
R_2 = OMe, OEt
R_3 = aryl, alkyl, alkenyl

The preparation of tertiary amines can be accomplished in a single step by combining urea with alkyl halides in the presence of sodium hydroxide under pressure at elevated temperatures (eq 31).[49]

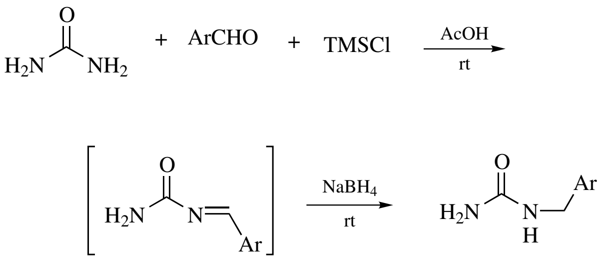


$2\ R_3N$ + salts + alcohols/ether (31)

yields 58–82%

R = allyl, crotyl, butyl, methallyl, octyl, benzyl

The reductive alkylation of urea to provide aryl substituted ureas has been disclosed.[50] Aryl aldehydes react with urea in the presence of TMSCl and AcOH to provide the intermediate imine, which is then reduced with $NaBH_4$ to provide alkylated ureas (eq 32). To obtain the mono-substituted alkylation product a large excess of urea (20 equiv) must be used. The excess is easily removed during work up.

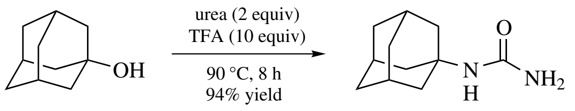


(32)

The hindered alcohols 4,4′-dimethoxybenzhydrol[51] and 1-adamantanol[52] undergo a hydroxyl substitution reaction with urea in acidic media to provide the corresponding *N*-substituted ureas (eqs 33 and 34). The substitution reaction is likely to occur through the generation of a carbenium ion.

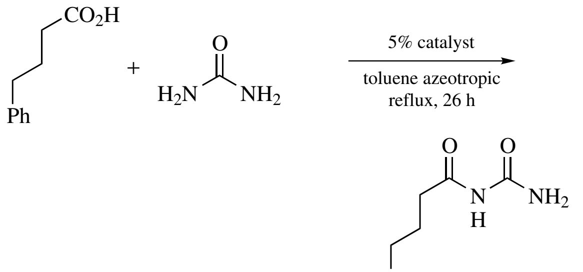
$$\mathrm{Ar_2CHOH} \xrightarrow[\text{20 °C, 15 h, 75\% yield}]{\text{urea, AcOH, cat H}_2\text{SO}_4} \mathrm{Ar_2CHNHCONH_2} \qquad (33)$$

Ar = 4-MeOC$_6$H$_4$



(34)

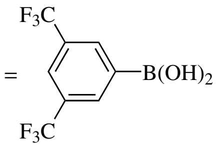
The direct condensation of carboxylic acids with urea can be accomplished catalytically in the presence of arylboronic acids to generate *N*-acylurea.[53] Condensation of the arylboronic acid with carboxylic acids generates an (acyloxy)boron complex. Subsequent nucleophilic attack by the urea nitrogen provides the *N*-acylurea (eq 35).



(35)

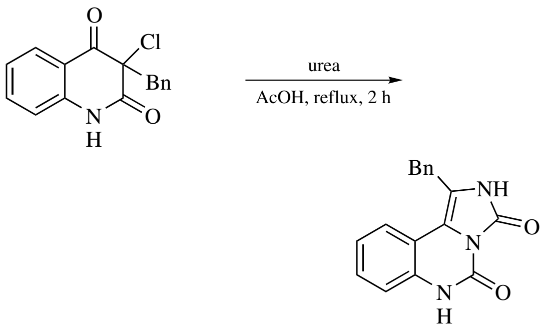
92% yield

catalyst =



A very interesting rearrangement product is observed when reacting 3-chloro-1*H*,3*H*-quinoline-2,4-diones with urea in

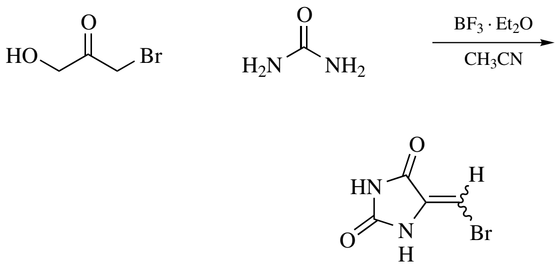
AcOH heated at reflux.[54] Instead of making the expected imidazo [4,5-c]-quinolone, 2,6-dihydro-imidazo[1,5-c]quinazoline-3,5-diones are produced consistently in high yields (eq 36). The rearrangement is believed to proceed through an isocyanate mechanism.



71% yield

(36)

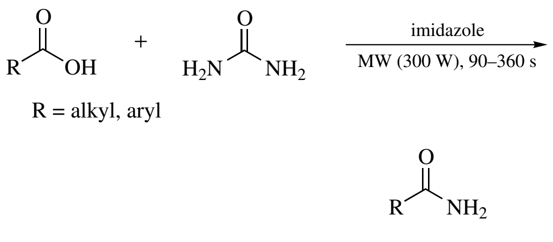
The reaction of bromopyruvic acid with urea in the presence of BF_3 provides 5-(bromomethylene)hydantoins (eq 37). The 5-(bromomethylene)hydantoins can subsequently react with a variety of nucleophiles to give 5-(substituted-methylene)hydantoins.[55]



47% yield

(37)

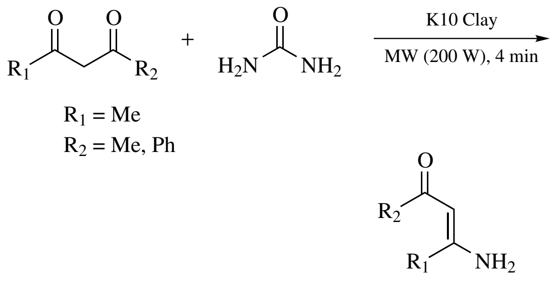
Microwave Assisted Transformations. A solvent-free procedure has been developed for the preparation of primary amides from urea and carboxylic acids using imidazole and microwave irradiation.[56] The reaction is believed to proceed through generation of the imidazolium carboxylate salt followed by displacement with ammonia that is liberated from urea under the reaction conditions (eq 38).



47–88% yield

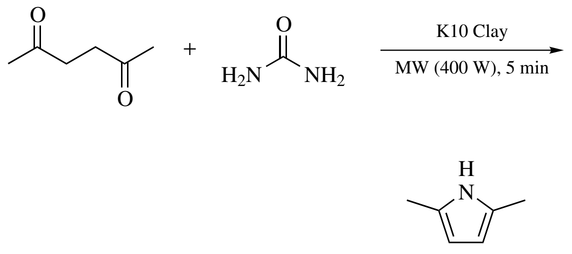
(38)

Another reaction that involves the production of ammonia from urea is the solvent-free reaction with dicarbonyl compounds in the presence of montmorillonite K10 clay under microwave conditions.[57] Reactions with β-diketones provide enamino ketones and reactions with γ-diketones give *N*-unsubstituted pyrroles (eqs 39 and 40).



54–99% yield

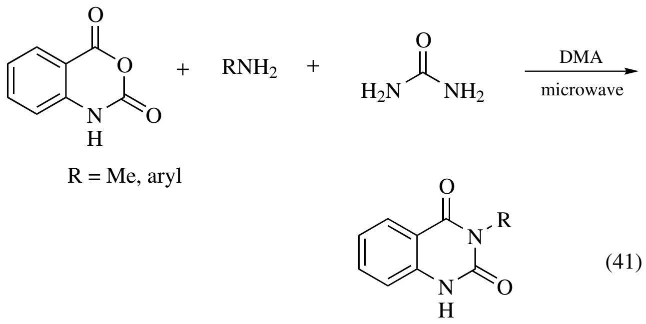
(39)



60% yield

(40)

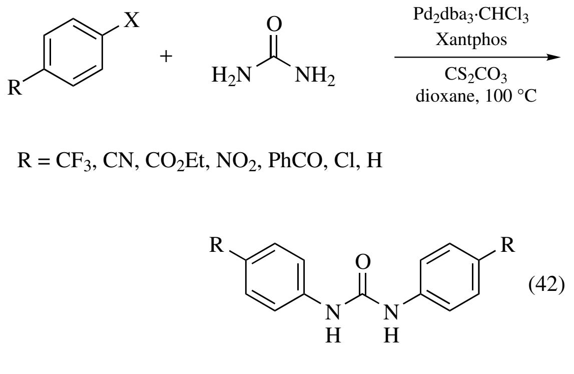
The condensation of isatoic anhydride with primary amines and urea in the presence of *N*,*N*-dimethyl acetamide (DMA) under microwave irradiation proceeds rapidly to form the corresponding quinazolinediones (eq 41).[58]



72–93% yield

(41)

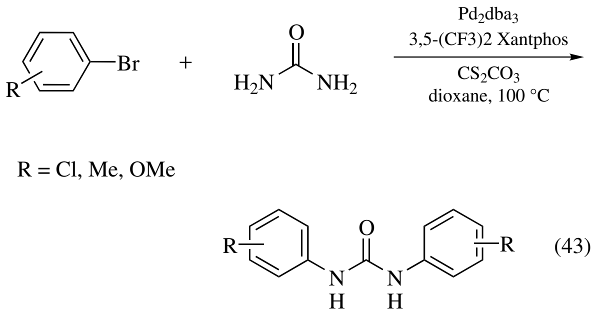
Metal-mediated Catalysis. Alkyl halides can be coupled with urea in the presence of 1 mol % $Pd_2dba_3 \cdot CHCl_3$, Xantphos ligand, and Cs_2CO_3 as a base to give *N*,*N*′-diarylureas.[59] The reaction is general for aryl bromides and aryl iodides containing electron-withdrawing groups at *para* postion (eq 42). The use of 3,5-$(CF_3)_2$Xantphos as a ligand allows the coupling of *ortho*- and, in limited cases, *meta*-substituted aryl bromides as well (eq 43).[60]



R = CF_3, CN, CO_2Et, NO_2, PhCO, Cl, H

(42)

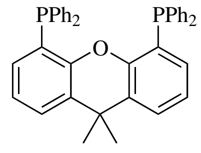
64–92% yield



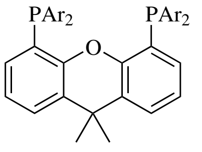
R = Cl, Me, OMe

(43)

62–91% yield



Xantphos



Ar = 3,5–$(CF_3)_2C_6H_3$

3,5-$(CF_3)_2$Xantphos

Catalytic amidations of aryl halides can also be performed using substituted ureas.[60,61]

Related Reagents. Hydrogen Peroxide–Urea.

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1. *Fieser & Fieser* **1967**, *1*, 1262.
2. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988; p 305.
3. (a) Bruson, H. A. U.S. Patent,1 989 968, 1935 (*Chem. Abstr.* **1935**, *29*, 1833). (b) D'Alelio, G. F.; Reid, E. E. U.S. Patent, 2 109 941, 1938 (*Chem. Abstr.* **1938**, *35*, 3419).
4. Biggs, B. S.; Bishop, W. S., *Org. Synth., Coll. Vol.* **1955**, *3*, 768.
5. Prabhakaran, P. V.; Jayadev, S.; Nema, S. K.; Rao, K. V. C., *Indian J. Chem., Sect. B* **1991**, *30B*, 1072.
6. (a) Smith, L. I.; Emerson, O. H., *Org. Synth., Coll. Vol.* **1955**, *3*, 151. (b) Pearson, D. E.; Baxter, J. F.; Carter, K. N., *Org. Synth., Coll. Vol.* **1955**, *3*, 154; see also Ref. 7.
7. Klimochkin, Yu. N.; Moiseev, I. K., *J. Org. Chem. USSR (Engl. Transl.)* **1987**, *23*, 1790 (*Zh. Org. Khim.* **1987**, *23*, 2026).
8. Bredereck, H.; Effenberger, F.; Hofmann, A., *Chem. Ber.* **1964**, *97*, 61 (*Chem. Abstr.* **1964**, *60*, 5501a).
9. Sakellariou, R.; Spéziale, V.; Hamdi, S., *Synth. Commun.* **1990**, *20*, 3443.
10. Donahoe, H. B.; Vanderwerf, C. A., *Org. Synth., Coll. Vol.* **1963**, *4*, 157.
11. Zav'yalov, S. I.; Sitkareva, I. V.; Ezhova, G. I.; Dorofeeva, O. V.; Zavozin, A. G.; Rumyantseva, E. E., *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1990**, 1297.
12. Mizutani, M.; Sanemitsu, Y.; Tamaru, Y.; Yoshida, Z., *Tetrahedron* **1986**, *42*, 305.
13. Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z., *J. Am. Chem. Soc.* **1988**, *110*, 3994.
14. (a) Slezak, F. B.; Hirsch, A.; Rosen, I., *J. Org. Chem.* **1960**, *25*, 660. (b) Grillon, E.; Gallo, R.; Pierrot, M.; Boileau, J.; Wimmer, E., *Tetrahedron Lett.* **1988**, *29*, 1015.
15. (a) Bakibaev, A. A.; Yagovkin, A. Yu.; Filimonov, V. D., *J. Org. Chem. USSR (Engl. Transl.)* **1991**, *27*, 1326 (*Zh. Org. Khim.* **1991**, *27*, 1512). (b) Butler, A. R.; Leitch, E., *J. Chem. Soc., Perkin Trans. 2* **1980**, 103. (c) Butler, A. R.; Hussain, I.; Leitch, E., *J. Chem. Soc., Perkin Trans. 2* **1980**, 106.
16. (a) Butler, A. R.; Leitch, E., *J. Chem. Soc., Perkin Trans. 2* **1977**, 1972. (b) Dunnavant, W. R.; James, F. L., *J. Am. Chem. Soc.* **1956**, *78*, 2740. (c) Page, P. C. B.; Graham, A. E.; Park, B. K., *Tetrahedron* **1992**, *48*, 7265. (d) Breur, A.; Zincke, T., *Liebigs Ann. Chem.* **1879**, *198*, 141.
17. Zalesov, V. S.; Andreichikov, Yu. S.; Nalimova, Yu. A.; Tendryakova, S. P.; Starkova, S. M.; Podushkina, N. A., *Pharm. Chem. J.* **1978**, *12*, 906 (translated from *Khim.-Farm. Zh.* **1978**, *12*, 93).
18. Murray, J. I., *Org. Synth., Coll. Vol.* **1963**, *4*, 744.
19. Dickey, J. B.; Gray, A. R., *Org. Synth., Coll. Vol.* **1943**, *2*, 60.
20. Ankhiwala, M. D., *J. Inst. Chem. (India)* **1990**, *62*, 67.
21. Donleavy, J. J.; Kise, M. A., *Org. Synth., Coll. Vol.* **1943**, *2*, 422.
22. (a) Biginelli, P., *Chem. Ber.* **1891**, *24*, 1317. (b) Folkers, K.; Harwood, H. J.; Johnson, T. B., *J. Am. Chem. Soc.* **1932**, *54*, 3751. (c) Jani, M. K.; Undavia, N. K.; Trivedi, P. B., *J. Indian Chem. Soc.* **1990**, *67*, 847.
23. (a) Chawla, H. M.; Pathak, M., *Tetrahedron* **1990**, *46*, 1331. (b) Corson, B. B.; Freeborn, E., *Org. Synth., Coll. Vol.* **1943**, *2*, 231.
24. Patel, H. V.; Fernandes, P. S., *Indian J. Chem., Sect. B* **1989**, *28B*, 782.
25. El-Rayyes, N. R.; Ramadan, H. M., *J. Heterocycl. Chem.* **1987**, *24*, 589.
26. Zee-Cheng, K.-Y.; Robins, R. K.; Cheng, C. C., *J. Org. Chem.* **1961**, *26*, 1877.
27. (a) Reichardt, C.; Budnik, U., *Chem. Ber.* **1990**, *123*, 2023 (*Chem. Abstr.* **1990**, *113*, 174 068v). (b) Gerus, I. I.; Vdovenko, S. I.; Gorbunova, M. G.; Kukhar, V. P., *Chem. Heterocycl. Compd. (Engl. Transl.)* **1991**, 398 (translated from *Khim. Geterotsikl. Soedin.* **1991**, 502).
28. Arukwe, J.; Keilen, G.; Undheim, K., *Acta Chem. Scand.* **1988**, *B42*, 530.
29. Abdel Galil, F. M.; Saleh, S. S., *Sulfur Lett.* **1989**, *9*, 9.
30. El-Bahaie, S.; El-Deeb, A.; Assy, M. C., *Pharmazie* **1991**, *46*, 26.
31. Sherman, W. R.; Taylor, E. C., Jr., *Org. Synth., Coll. Vol.* **1963**, *4*, 247.
32. Lavrov, V. I.; Parshina, L. N.; Nedolya, N. A.; Papsheva, N. P.; Stankevich, V. K.; Kukharev, B. F., *J. Org. Chem. USSR (Engl. Transl.)* **1990**, *26*, 216 (*Zh. Org. Khim.* **1990**, *26*, 259).
33. (a) Sankhavasi, W.; Yamamoto, M.; Kohmoto, S.; Yamada, K., *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1425, and references cited therein. (b) Yanborisova, O. A.; Konshin, M. E., *Chem. Heterocycl. Compd. (Engl. Transl.)* **1991**, 390 (translated from *Khim. Geterotsikl. Soedin.* **1991**, 493).
34. Aichaoui, H.; Poupaert, J. H.; Lesieur, D.; Hé Nichart, J.-P., *Tetrahedron* **1991**, *47*, 6649.
35. (a) Close, W. J., *J. Org. Chem.* **1950**, *15*, 1131. (b) Batra, S.; Sharma, S., *Indian J. Chem., Sect. B* **1991**, *30B*, 327.
36. (a) Roder, H.; Helmchen, G.; Peters, E.-M.; Peters, K.; Schnering, H.-G. V., *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 898. (b) Melnyk, O.; Stephan, E.; Pourcelot, G.; Cresson, P., *Tetrahedron* **1992**, *48*, 841. (c) Cardillo, G.; Orena, M.; Romero, M.; Sandri, S., *Tetrahedron* **1989**, *45*, 1501. (d) Cardillo, G.; d'Amico, A.; Orena, M.; Sandri, S., *J. Org. Chem.* **1988**, *53*, 2354. See ref. 33(a).

37. (a) Middleton, W. J.; Engelhardt, V. A.; *J. Am. Chem. Soc.* **1958**, *80*, 2788. (b) Dickinson, C. L.; Melby, L. R., *Org. Synth., Coll. Vol.* **1963**, *4*, 276.
38. (a) Hagan, M. *Clathrate Inclusion Compounds*; Reinhold: New York, 1962. (b) Takemoto, K.; Sonoda, N. *Inclusion Compounds*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D., Eds; Academic: London, 1984; Vol. 2, p 47.
39. (a) Bengen, M. F.; Schlenk, W., Jr., *Experientia* **1949**, *5*, 200 (*Chem. Abstr.* **1950**, *44*, 1910). (b) Bengen, M. F., *Angew. Cheml* **1951**, *63*, 207 (*Chem. Abstr.* **1951** *45*, 1910b). (c) Schlenk, W., *Justus Liebigs Ann. Chem.* **1949**, *565*, 204 (*Chem. Abstr.* **1950**, *44*, 3900). (d) Zimmerschied, W. J.; Dinerstein, R. A.; Weitkamp, A. W.; Marschner, R. F., *Ind. Eng. Chem.* **1950**, *42*, 1300.
40. Sergienko, S. R.; Ovezov, A. A.; Aidogdyev, A., *Dokl. Akad. Nauk SSSR* **1975**, *223*, 1150 (*Chem. Abstr.* **1975**, *83*, 192 506c).
41. Swern, D.; Witnauer, L. P.; Knight, H. B., *J. Am. Chem. Soc.* **1952**, *74*, 1655.
42. Kappe, C. O., *Eur. J. Med. Chem* **2000**, *35*, 1043.
43. (a) Dondoni, A.; Massi, A.; Minghini, E.; Sabbatini, S.; Bertolasi, V., *J. Org. Chem.* **2003**, *68*, 6172. (b) Ranu, B. C.; Hajra, A.; Jana, U., *J. Org. Chem.* **2000**, *65*, 6270. (c) Hu, E. H.; Sidler, D. R.; Dolling, U., *J. Org. Chem.* **1998**, *63*, 3454.
44. (a) Hazarkhani, H.; Karimi, B., *Synthesis* **2004**, 1239. (b) Kappe, C. O.; Kumar, D.; Varma, R. S., *Synthesis* **1999**, 1799.
45. (a) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Fard, M. A. B., *Heterocycles* **2003**, *60*, 2435. (b) Ranu, B. C.; Hajra, A.; Dey, S. S., *Org. Process Res. Dev.* **2002**, *6*, 817. (c) Bose, D. S.; Fatima, L.; Mereyala, H. B., *J. Org. Chem.* **2003**, *68*, 587.
46. (a) Dondoni, A.; Massi, A., *Tetrahedron Lett.* **2001**, *42*, 7975. (b) Xia, M.; Wang, Y.-G., *Tetrahedron Lett.* **2002**, *43*, 7703.
47. (a) Simon, C.; Constantieux, T.; Rodriuez, J., *Eur. J. Org. Chem.* **2004**, 4957. (b) Kappe, C. O.; Stadler, A., *Org. React.* **2004**, *63*, 1. (c) Kappe, C. O., *Acc. Chem. Res.* **2000**, *33*, 879.
48. Aron, Z. D.; Overman, L. E., *Chem. Commun.* **2004**, 253.
49. Sachinvala, N. N.; Winsor, D. L.; Maskos, K.; Grimm, C.; Hamed, O.; Vigo, T. L.; Bertoniere, N. R., *J. Org. Chem.* **2000**, *65*, 9234.
50. Xu, D.; Ciszewski, L.; Li., T.; Repič, O.; Blacklock, T. J., *Tetrahedron Lett.* **1998**, *39*, 1107.
51. Henneuse, C.; Boxus, T.; Tesolin, L.; Guiseppe, P.; Marchand-Brynaert, J., *Synthesis* **1996**, 495.
52. Shokova, E.; Mousoulou, T.; Luzikov, Y.; Kovalev, V., *Synthesis* **1997**, 1034.
53. Maki, T.; Ishihara, K.; Yamanoto, H., *Synlett* **2004**, 1355.
54. Klásek, A.; Kořistek, K.; Lyčka, A.; Holčapek, M., *Tetrahedron* **2003**, *59*, 1283.
55. Mathur, N. C.; Wong, S. K.; Shechter, H., *Tetrahedron Lett.* **2003**, *44*, 5141.
56. Khalafi-Nezhad, H.; Mokhtari, B.; Rad, M. N. S., *Tetrahedron Lett.* **2003**, *44*, 7325.
57. Ruault, P.; Pilard, J.-F.; Touaux, B.; Texier-Bouilet, F.; Hamelin, J., *Synlett* **1994**, 935.
58. Azizian, J.; Mohammadi, A. A.; Karimi, A. R., *Synth. Commun.* **2003**, *33*, 415.
59. Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P., *Tetrahedron Lett.* **2001**, *42*, 4381.
60. Sergeev, A. G.; Artamkina, G. A.; Beletskaya, I. P., *Tetrahedron Lett.* **2003**, *44*, 4719.
61. See ref. 60 and Yin, J; Buchwald, S. L., *J. Am. Chem. Soc.* **2002**, *124*, 6043.

Urushibara Nickel[1]

Ni

[7440-02-0] Ni (MW 58.69)
InChI = 1/Ni
InChIKey = PXHVJJICTQNCMI-UHFFFAOYAH

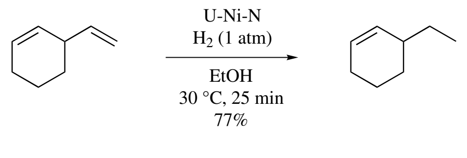
(precipitated metal hydrogenation catalyst; useful principally in reduction of alkynes and alkenes to alkanes,[2] reduction of carbonyls to alcohols,[3] dehydrogenations,[1] and reductive desulfurizations[1])

Preparative Methods: Urushibara catalysts are prepared by acid (U-Ni-A), base (U-Ni-B), or neutral (U-Ni-N) digestion of precipitated nickel. Similar catalysts can be prepared using either iron or cobalt.[1]

Handling, Storage, and Precautions: Urushibara catalysts do not appear to degrade upon short exposure to air.[4] Protection from moisture is required for long-term storage.

Urushibara Catalysts. The Urushibara catalysts are a family of precipitated metal catalysts that have been compared to the more common ***Raney Nickel*** catalysts. Although the two can catalyze many of the same reactions, Urushibara metals offer several advantages: they are nonpyrophoric, are easily generated, have a long shelf life, and can catalyze highly regio- and stereoselective reductions.

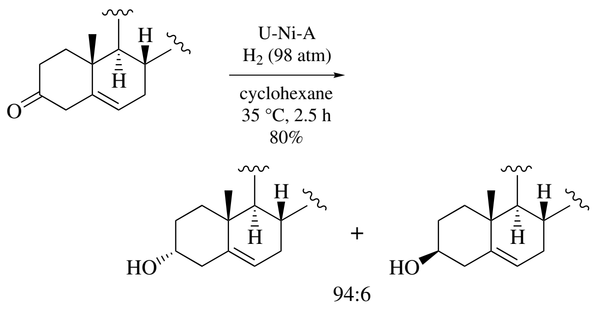
Catalytic Hydrogenation of Alkynes and Alkenes. Alkenes and alkynes can be reduced to the corresponding alkanes using moderate to high pressures of H_2 and temperatures. In eq 1, the exocyclic alkene is hydrogenated selectively with the use of U-Ni-N. Longer hydrogenation times and use of other Urushibara catalysts result in complete reduction of this substrate. The use of Raney nickel in this example results in nonspecific reduction.[2] Aromatic rings can also be saturated; however, these reactions only proceed at high temperature or under pressure.[1]



(1)

Catalytic Hydrogenation of Carbonyl Compounds. Ketones and aldehydes can be reduced to their respective alcohols using Urushibara catalysts with hydrogen at atmospheric pressure and room temperature. eq 2 demonstrates the regio- and stereoselectivity that can be obtained using Urushibara catalysts.[3] Use of Raney nickel results in an equimolar mixture of the two stereoisomers. Hydrogenolysis of the resulting C–O bond can occur with aryl-substituted compounds, giving the corresponding hydrocarbons.[1]

Dehydrogenations. Urushibara catalysts have been used as dehydrogenation catalysts. Numerous examples exist with steroidal compounds using cyclohexanone as the hydrogen acceptor. In general, dehydrogenations using Urushibara catalysts are comparable to those of Raney nickel.[1]



(2)

Reductive Desulfurizations. Urushibara catalysts, specifically U-Ni-A, have been used in desulfurizations of sulfur-containing compounds such as thiols, sulfides, disulfides, and thioacetals without competing reduction of alkenes. Reductive desulfurizations can be performed using Raney nickel with comparable yields.[1]

Miscellaneous Reductions. Urushibara catalysts have been employed to reduce oximes, nitriles, hydroxylamines, nitro, and nitroso compounds. These reductions can be very dependent on reaction conditions. Yields of products are generally high and steric biasing can lead to high levels of stereocontrol.[1]

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1. (a) Hata, K. *New Hydrogenating Catalysts*; Halsted: New York, 1971. (b) Hata, K.; Motoyama, I., *Org. Prep. Proced. Int.* **1972**, *4*, 179. (c) Shiota, M., *Strem Chem.* **1975**, *III*, 13.
2. (a) Kajitani, M.; Okada, J.; Ueda, T.; Sugimori, A.; Urushibara, Y., *Chem. Lett.* **1973**, 777. (b) Kajitani, M.; Sasaki, Y.; Okada, J.; Ohmura, K.; Sugimori, A.; Urushibara, Y., *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1203.
3. (a) Ishige, M.; Shiota, M., *Synthesis* **1973**, 171. (b) Ishige, M.; Shiota, M.; Suzuki, F., *Can. J. Chem.* **1976**, *54*, 2581. (c) Ishige, M.; Shiota, M., *Can. J. Chem.* **1975**, *53*, 1700.
4. Ishige, M.; Shiota, M., *Can. J. Chem.* **1975**, *53*, 1700.

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