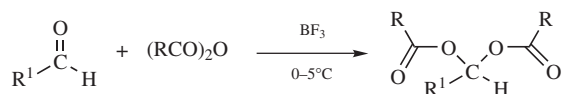


OS I, 1, 298, 364, 381; II, 137; III, 123, 387, 502, 536, 644, 731, 800; IV, 21, 479, 679; V, 5, 292, 303, 450, 539; VI, 567, 666, 954; VII, 59, 149, 168, 177, 241, 271, 297; VIII, 357. Also see OS IV, 558, 588; V, 25; VIII, 415.

16-6 Acylation of Aldehydes and Ketones

O-Acyl-*C*-acyloxy-addition

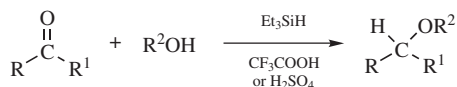


Aldehydes can be converted to *acylals* by treatment with an anhydride in the presence of BF_3 , proton acids,¹⁶⁴ PCl_3 ,¹⁶⁵ NBS ,¹⁶⁶ LiBF_4 ,¹⁶⁷ FeCl_3 ,¹⁶⁸ InCl_3 ,¹⁶⁹ InBr_3 ,¹⁷⁰ $\text{Cu}(\text{OTf})_2$,¹⁷¹ $\text{Bi}(\text{OTf})_3$,¹⁷² BiCl_3 ,¹⁷³ $\text{Bi}(\text{NO}_3)_3$,¹⁷⁴ WCl_6 ,¹⁷⁵ ZrCl_4 ,¹⁷⁶ ceric ammonium nitrate,¹⁷⁷ With Envirocat EPZ10 and microwave irradiation, acetic anhydride react with aldehydes to give the acylal.¹⁷⁸ Conjugated aldehydes are converted to the corresponding acylal by reaction with acetic anhydride and a FeCl_3 catalyst.¹⁷⁹ The reaction cannot normally be applied to ketones, though an exception has been reported when the reagent is trichloroacetic anhydride, which gives acylals with ketones without a catalyst.¹⁸⁰

OS IV, 489.

16-7 Reductive Alkylation of Alcohols

C-Hydro-*O*-alkyl-addition



¹⁶⁴For example, see Olah, G.A.; Mehrotra, A.K. *Synthesis* **1982**, 962.

¹⁶⁵See Michie, J.K.; Miller, J.A. *Synthesis* **1981**, 824.

¹⁶⁶Karimi, B.; Seradj, H.; Ebrahimian, G.R. *Synlett* **2000**, 623

¹⁶⁷Sumida, N.; Nishioka, K.; Sato, T. *Synlett* **2001**, 1921; Yadav, J.S.; Reddy, B.V.S.; Venugopal, C.; Ramalingam, V.T. *Synlett* **2002**, 604.

¹⁶⁸Li, Y.-Q. *Synth. Commun.* **2000**, 30, 3913; Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* **2001**, 123, 3671; Wang, C.; Li, M. *Synth. Commun.* **2002**, 32, 3469.

¹⁶⁹Yadav, J.S.; Reddy, B.V.S.; Srinivas, Ch. *Synth. Commun.* **2002**, 32, 1175, 2169.

¹⁷⁰Yin, L.; Zhang, Z.H.; Wang, Y.-M.; Pang, M.-L. *Synlett* **2004**, 1727.

¹⁷¹Chandra, K.L.; Saravanan, P.; Singh, V.K. *Synlett* **2000**, 359.

¹⁷²Carrigan, M.D.; Eash, K.J.; Oswald, M.C.; Mohan, R.S. *Tetrahedron Lett.* **2001**, 42, 8133.

¹⁷³Mohammadpoor-Baltork, I.; Aliyan, H. *Synth. Commun.* **1999**, 29, 2741.

¹⁷⁴Aggen, D.H.; Arnold, J.N.; Hayes, P.D.; Smoter, N.J.; Mohan, R.S. *Tetrahedron* **2004**, 60, 3675.

¹⁷⁵A solvent-free reaction. See Karimi, B.; Ebrahimian, G.-R.; Seradj, H. *Synth. Commun.* **2002**, 32, 669.

¹⁷⁶Smitha, G.; Reddy, Ch.S. *Tetrahedron* **2003**, 59, 9571.

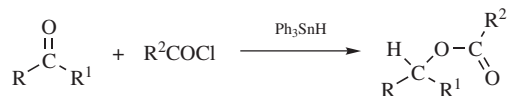
¹⁷⁷Roy, S.C.; Banerjee, B. *Synlett* **2002**, 1677.

¹⁷⁸Bandgar, B.P.; Makone, S.S.; Kulkarni, S.R. *Monat. Chem.* **2000**, 131, 417.

¹⁷⁹Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* **2001**, 123, 3671.

¹⁸⁰Libman, J.; Sprecher, M.; Mazur, Y. *Tetrahedron* **1969**, 25, 1679.

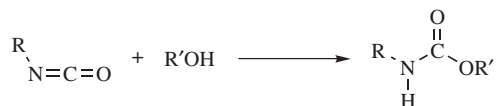
Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid¹⁸¹ or by hydrogenation in alcoholic acid in the presence of platinum oxide.¹⁸² The process can formally be regarded as addition of ROH to give a hemiacetal, $RR'C(OH)OR^2$, followed by reduction of the OH. In this respect, it is similar to **16-17**. The reaction of an aldehyde with $BuOSiHMe_2$ and a Me_3SiI catalyst gives the corresponding butyl alkyl ether.¹⁸³ In a similar reaction, ketones can be converted to carboxylic esters (reductive acylation of ketones) by treatment with an acyl chloride and triphenyltin hydride.¹⁸⁴



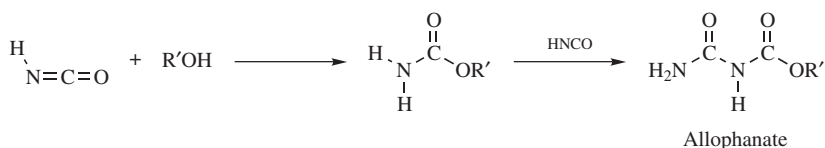
Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone \rightarrow dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.¹⁸⁵

16-8 The Addition of Alcohols to Isocyanates

N-Hydro-C-alkoxy-addition



Carbamates (substituted urethanes) are prepared when isocyanates are treated with alcohols. This is an excellent reaction, of wide scope, and gives good yields. Isocyanic acid HNCO gives unsubstituted carbamates. Addition of a second equivalent of HNCO gives *allophanates*.



The isocyanate can be generated *in situ* by the reaction of an amine and oxalyl chloride, and subsequent reaction with HCl and then an alcohol gives the carbamate.¹⁸⁶ Polyurethanes are made by combining compounds with two NCO groups with

¹⁸¹Doyle, M.P.; DeBruyn, D.J.; Kooistra, D.A. *J. Am. Chem. Soc.* **1972**, *94*, 3659.

¹⁸²Verzele, M.; Acke, M.; Anteunis, M. *J. Chem. Soc.* **1963**, 5598. For still another method, see Loim, L.M.; Parnes, Z.N.; Vasil'eva, S.P.; Kursanov, D.N. *J. Org. Chem. USSR* **1972**, *8*, 902.

¹⁸³Miura, K.; Ootsuka, K.; Suda, S.; Nishikori, H.; Hosomi, A. *Synlett* **2002**, 313.

¹⁸⁴Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 4970.

¹⁸⁵Sassaman, M.B.; Kotian, K.D.; Prakash, G.K.S.; Olah, G.A. *J. Org. Chem.* **1987**, *52*, 4314. See also, Kikugawa, Y. *Chem. Lett.* **1979**, 415.

¹⁸⁶Oh, L.M.; Spoors, P.G.; Goodman, R.M. *Tetrahedron Lett.* **2004**, *45*, 4769.

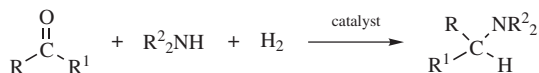
aliphatic aldehyde.³²⁵ The reaction is a combination of **16-15** and **17-29**. Direct nitrile formation has also been accomplished with certain derivatives of NH_2OH , notably, $\text{NH}_2\text{OSO}_2\text{OH}$.³²⁶ Treatment with hydroxylamine and NaI ³²⁷ or certain carbonates³²⁸ also converts aldehydes to the nitrile. Another method involves treatment with hydrazoic acid, though the Schmidt reaction (**18-16**) may compete.³²⁹ Aromatic aldehydes have been converted to nitriles in good yield with $\text{NH}_2\text{OH}/\text{HCOOH}$ on silica gel.³³⁰ Microwave irradiation has been used with $\text{NH}_2\text{OH}\cdot\text{HCl}$ and another reagent, which includes phthalic anhydride,³³¹ $\text{Bu}_2\text{SnO}\cdot\text{Al}_2\text{O}_3$,³³² or $\text{H}-\text{Y}$ zeolite.³³³ Other reagents include *N*-phenylurea with tosic acid,³³⁴ MnO_2 and ammonia,³³⁵ I_2 with aqueous ammonia,³³⁶ dimethylhydrazine followed by dimethyl sulfoxide,³³⁷ trimethylsilyl azide,³³⁸ and with hydroxylamine hydrochloride, MgSO_4 , and TsOH .³³⁹ The reaction of a conjugated aldehyde with ammonia, CuCl and 50% H_2O_2 gave the conjugated nitrile.³⁴⁰ Benzylic alcohols can be oxidized in the presence of ammonia to give the nitrile.³⁴¹ Trichloroisocyanuric acid with a catalytic amount of TEMPO (p. 274) converts aldehydes to nitriles at 0°C in dichloromethane.³⁴²

On treatment with 2 equivalents of dimethylaluminum amide Me_2AlNH_2 , carboxylic esters can be converted to nitriles: $\text{RCOOR}' \rightarrow \text{RCN}$.³⁴³ This is very likely a combination of **16-75** and **17-30**. See also, **19-5**.

OS V, 656.

16-17 Reductive Alkylation of Ammonia or Amines

Hydro,dialkylamino-de-oxo-bisubstitution



³²⁵Sharghi, H.; Sarvari, M.H. *Tetrahedron* **2002**, 58, 10323. With wet alumina followed by MeSO_2Cl the product is an amide.

³²⁶Streith, J.; Fizet, C.; Fritz, H. *Helv. Chim. Acta* **1976**, 59, 2786.

³²⁷Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* **2003**, 1841.

³²⁸Bose, D.S.; Goud, P.R. *Synth. Commun.* **2002**, 32, 3621.

³²⁹For additional methods, see Gelas-Mialhe, Y.; Vessière, R. *Synthesis* **1980**, 1005; Arques, A.; Molina, P.; Soler, A. *Synthesis* **1980**, 702; Sato, R.; Itoh, K.; Itoh, K.; Nishina, H.; Goto, T.; Saito, M. *Chem. Lett.* **1984**, 1913; Reddy, P.S.N.; Reddy, P.P. *Synth. Commun.* **1988**, 18, 2179; Neunhoeffer, H.; Diehl, W.; Karafiat, U. *Liebigs Ann. Chem.* **1989**, 105.

³³⁰Kabalka, G.W.; Yang, K. *Synth. Commun.* **1998**, 28, 3807.

³³¹Veveřková, E.; Toma, Š. *Synth. Commun.* **2000**, 30, 3109.

³³²Yadav, J.S.; Reddy, B.V.S.; Madan, Ch. *J. Chem. Res. (S)* **2001**, 190.

³³³Srinivas, K.V.N.S.; Reddy, E.B.; Das, B. *Synlett* **2002**, 625.

³³⁴Cokun, N.; Arikian, N. *Tetrahedron* **1999**, 55, 11943.

³³⁵Lai, G.; Bhamare, N.K.; Anderson, W.K. *Synlett* **2001**, 230.

³³⁶Talukdar, S.; Hsu, J.-L.; Chou, T.-C.; Fang, J.-M. *Tetrahedron Lett.* **2001**, 42, 1103.

³³⁷Kamal, A.; Arifuddin, M.; Rao, N.V. *Synth. Commun.* **1998**, 28, 4507.

³³⁸Nishiyama, K.; Oba, M.; Watanabe, A. *Tetrahedron* **1987**, 43, 693.

³³⁹Ganboa, I.; Palomo, C. *Synth. Commun.* **1983**, 13, 219.

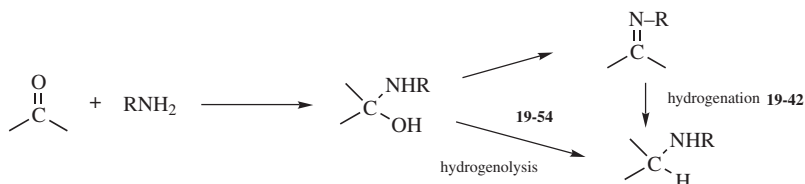
³⁴⁰Erman, M.B.; Snow, J.W.; Williams, M.J. *Tetrahedron Lett.* **2000**, 41, 6749.

³⁴¹See Baxendale, I.R.; Ley, S.V.; Sneddon, H.F. *Synlett* **2002**, 775; McAllister, G.D.; Wilfred, C.D.; Taylor, R.J.K. *Synlett* **2002**, 1291.

³⁴²Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* **2003**, 2629.

³⁴³Wood, J.L.; Khatri, N.A.; Weinreb, S.M. *Tetrahedron Lett.* **1979**, 4907.

When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen and a hydrogenation catalyst (heterogeneous or homogeneous),³⁴⁴ *reductive alkylation* of ammonia or the amine (or *reductive amination* of the carbonyl compound) takes place.³⁴⁵ The reaction can formally be regarded as occurring in the following manner (shown for a primary amine), which probably does correspond to the actual sequence of steps:³⁴⁶ In this regard, the reaction of an aldehyde with an amine to give an iminium salt (**16-31**) can be followed in a second chemical step of reduction of the C=N unit (**19-42**) using NaBH₄ or a variety of other reagents.³⁴⁷



Primary amines have been prepared from many aldehydes with at least five carbons and from many ketones by treatment with ammonia and a reducing agent. Smaller aldehydes are usually too reactive to permit isolation of the primary amine. Secondary amines have been prepared by both possible procedures: 2 equivalents of ammonia and 1 equivalent of aldehyde or ketone, and 1 equivalent of primary amine and 1 equivalent of carbonyl compound, the latter method being better for all but aromatic aldehydes. Tertiary amines can be prepared in three ways, but the method is seldom carried out with 3 equivalents of ammonia and 1 equivalent of carbonyl compound. Much more often they are prepared from primary or secondary amines.³⁴⁸ When the reagent is ammonia, it is possible for the initial product to react again and for this product to react again, so that secondary and tertiary amines are usually obtained as side products. Similarly, primary amines give tertiary as well as secondary amines. In order to minimize this, the aldehyde or ketone is treated with an excess of ammonia or primary amine (unless of course the higher amine is desired).

For ammonia and primary amines there are two possible pathways, but when secondary amines are involved, only the hydrogenolysis pathway is possible. The reaction is compatible with amino acids, giving the *N*-alkylated amino acid.³⁴⁹

³⁴⁴Rh: Kadyrov, R.; Riermeier, T.H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, 68, 4067; Gross, T.; Seayad, A.M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, 4, 2055. Ir: Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, 68, 4120.

³⁴⁵For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, **1985**, pp. 82–93; Klyuev, M.V.; Khidekel, M.L. *Russ. Chem. Rev.* **1980**, 49, 14; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, **1967**, pp. 291–303.

³⁴⁶See, for example, Le Bris, A.; Lefebvre, G.; Coussemant, F. *Bull. Soc. Chim. Fr.* **1964**, 1366, 1374, 1584, 1594.

³⁴⁷For a simple example see, Bhattacharyya, S. *Synth. Commun.* **2000**, 30, 2001.

³⁴⁸For a review of the preparation of tertiary amines by reductive alkylation, see Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, **1965**, pp. 44–52.

³⁴⁹Song, Y.; Sercel, A.D.; Johnson, D.R.; Colbry, N.L.; Sun, K.-L.; Roth, B.D. *Tetrahedron Lett.* **2000**, 41, 8225.

Other reducing agents³⁵⁰ can be used instead of hydrogen and a catalyst, among them zinc and HCl, B₁₀H₁₄³⁵¹ or B₁₀H₁₄ with Pd/C,³⁵² a picolinyl borane complex in acetic acid–methanol,³⁵³ PhSiH₃ with 2% Bu₂SnCl₂,³⁵⁴ and polymethylhydrosiloxane.³⁵⁵ Several hydride reducing agents can be used, including NaBH₄³⁵⁶ sodium borohydride with Ti(OiPr)₄³⁵⁷ or NiCl₂,³⁵⁸ NaBH₄/H₃BO₄,³⁵⁹ borohydride-exchange resin,³⁶⁰ sodium cyanoborohydride (NaBH₃CN),³⁶¹ sodium triacetoxymethylborohydride,³⁶² or a polymer-bound triethylammonium acetoxymethylborohydride.³⁶³ A Hantzsch dihydropyridine in conjunction with a scandium catalyst has been used.³⁶⁴ An interesting variation uses a benzylic alcohol in a reaction with a primary amine, and a mixture of MnO₂ and NaBH₄, giving *in situ* oxidation to the aldehyde and reductive amination to give the amine as the final product.³⁶⁵

Formic acid is commonly used for reductive amination³⁶⁶ in what is called the *Wallach reaction*. Secondary amines react with formaldehyde and NaH₂PO₃ to give the *N*-methylated tertiary amine³⁶⁷ and microwave irradiation has also been used.³⁶⁸ Conjugated aldehydes are converted to alkenyl-amines with the amine/silica gel followed by reduction with zinc borohydride.³⁶⁹ In the particular case where primary or secondary amines are reductively methylated with formaldehyde and formic acid, the method is called the *Eschweiler–Clarke procedure*. Heating with paraformaldehyde and oxalyl chloride has been used to give the same result.³⁷⁰ It is

³⁵⁰For a list of many of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 835–840.

³⁵¹Bae, J.W.; Lee, S.H.; Cho, Y.J.; Yoon, C.M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 145.

³⁵²Jung, Y.J.; Bae, J.W.; Park, E.S.; Chang, Y.M.; Yoon, C.M. *Tetrahedron* **2003**, 59, 10331.

³⁵³Sato, S.; Sakamoto, T.; Miyazawa, E.; Kitugawa, Y. *Tetrahedron* **2004**, 60, 7899.

³⁵⁴Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, 3, 1745.

³⁵⁵Chandrasekhar, S.; Reddy, Ch.R.; Ahmed, M. *Synlett* **2000**, 1655.

³⁵⁶Sondengam, B.L.; Hentchoya Hémo, J.; Charles, G. *Tetrahedron Lett.* **1973**, 261; Schellenberg, K.A. *J. Org. Chem.* **1963**, 28, 3259; Gribble, G.W.; Nutaitis, C.F. *Synthesis* **1987**, 709.

³⁵⁷Neidigh, K.A.; Avery, M.A.; Williamson, J.S.; Bhattacharyya, S. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2527; Bhattacharyya, S. *J. Org. Chem.* **1995**, 60, 4928.

³⁵⁸Saxena, I.; Borah, R.; Sarma, J.C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 503.

³⁵⁹This is a solvent-free reaction. See Cho, B.T.; Kang, S.K. *Synlett* **2004**, 1484.

³⁶⁰Yoon, N.M.; Kim, E.G.; Son, H.S.; Choi, J. *Synth. Commun.* **1993**, 23, 1595.

³⁶¹Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* **1971**, 93, 2897; Mattson, R.J.; Pham, K.M.; Leuck, D.J.; Cowen, K.A. *J. Org. Chem.* **1990**, 55, 2552. See also, Barney, C.L.; Huber, E.W.; McCarthy, J.R. *Tetrahedron Lett.* **1990**, 31, 5547. For reviews of NaBH₃CN, see Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* **1979**, 11, 201; Lane, C.F. *Synthesis* **1975**, 135.

³⁶²Abdel-Magid, A.F.; Maryanoff, C.A.; Carson, K.G. *Tetrahedron Lett.* **1990**, 31, 5595; Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* **1996**, 61, 3849.

³⁶³Bhattacharyya, S.; Rana, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* **2003**, 44, 4957.

³⁶⁴Itoh, T.; Nagata, K.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **2002**, 43, 3105; Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* **2004**, 60, 6649.

³⁶⁵Kanno, H.; Taylor, R.J.K. *Tetrahedron Lett.* **2002**, 43, 7337.

³⁶⁶For a microwave induced reaction see Torch, S.; Barbry, D. *J. Chem. Res. (S)* **2001**, 292.

³⁶⁷Davis, B.A.; Durden, D.A. *Synth. Commun.* **2000**, 30, 3353.

³⁶⁸Barbry, D.; Torch, S. *Synth. Commun.* **1996**, 26, 3919.

³⁶⁹Ranu, B.C.; Majee, A.; Sarkar, A. *J. Org. Chem.* **1998**, 63, 370.

³⁷⁰Rosenau, T.; Potthast, A.; Röhrling, J.; Hofinger, A.; Sixxa, H.; Kosma, P. *Synth. Commun.* **2002**, 32, 457.

possible to use ammonium (or amine) salts of formic acid,³⁷¹ or formamides, as a substitute for the Wallach conditions. This method is called the *Leuckart reaction*,³⁷² and in this case the products obtained are often the *N*-formyl derivatives of the amines instead of the free amines. A transition-metal catalyzed variation has been reported.³⁷³ Primary and secondary amines can be *N*-ethylated (e.g., $\text{ArNHR} \rightarrow \text{ArNREt}$) by treatment with NaBH_4 in acetic acid.³⁷⁴ Aldehydes react with aniline in the presence of Montmorillonite K10 clay and microwaves to give the amine.³⁷⁵ Tributyltin hydride is used with an ammonium salt,³⁷⁶ or $\text{Bu}_2\text{SnClH}\cdot\text{HMPA}$ with an aromatic amine,³⁷⁷ in the presence of a ketone to give the corresponding amine. Allylic silanes react with aldehydes and carbamates, in the presence of bismuth catalysts,³⁷⁸ or $\text{BF}_3\cdot\text{OEt}_2$ ³⁷⁹ to give the corresponding allylic *N*-carbamoyl derivative, and trityl perchlorate has been used for the same purpose when *N*-trimethylsilyl carbamates are employed.³⁸⁰ The reaction can be done with aromatic amines in the presence of vinyl ethers and a copper complex to give β -amino ketones.³⁸¹ Reductive amination of an aryl amine and an aryl aldehyde that contains a ortho conjugated ketone substituents gives the amine, which adds 1,4- (**15-AA**) to the α,β -unsaturated ketone unit to give a bicyclic amine.³⁸² Alternative methods of reductive alkylation have been developed. Alkylation of an imine formed *in situ* is also possible.³⁸³

Reductive alkylation has also been carried out on nitro, nitroso, azo, and other compounds that are reduced *in situ* to primary or secondary amines. Azo compounds react with aldehydes, in the presence of proline, and subsequent reduction with NaBH_4 gives the chiral hydrazine derivative.³⁸⁴

³⁷¹For a review of ammonium formate in organic synthesis, see Ram, S.; Ehrenkauffer, R.E. *Synthesis* **1988**, 91.

³⁷²For a review, see Moore, M.L. *Org. React.* **1949**, 5, 301. For discussions of the mechanism, see Awachie, P.I.; Agwada, V.C. *Tetrahedron* **1990**, 46, 1899, and references cited therein. For a microwave-induced variation, see Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J.M.; Domínguez, E.; Palomo, C. *Tetrahedron Lett.* **1996**, 37, 8177. For the effects of added formamide, see Lejon, T.; Helland, I. *Acta Chem. Scand.* **1999**, 53, 76.

³⁷³Using a rhodium catalyst, see Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* **2002**, 67, 8685. For a review of this reaction, see Riermeier, T.H.; Dingerdissen, U.; Börner, A. *Org. Prep. Proceed. Int.* **2004**, 36, 99.

³⁷⁴For a review, see Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proceed. Int.* **1985**, 17, 317, pp. 336–350.

³⁷⁵Varma, R.S.; Dahiya, R. *Tetrahedron* **1998**, 54, 6293.

³⁷⁶Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synlett* **2000**, 556.

³⁷⁷Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* **2000**, 556.

³⁷⁸Ollevier, T.; Ba, T. *Tetrahedron Lett.* **2003**, 44, 9003.

³⁷⁹Billet, M.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2001**, 42, 631.

³⁸⁰Niimi, L.; Serita, K.-i.; Hiraoka, S.; Yokozawa, T. *Tetrahedron Lett.* **2000**, 41, 7075.

³⁸¹Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, 64, 6833.

³⁸²Suwa, T.; Shibata, I.; Nishino, K.; Baba, A. *Org. Lett.* **1999**, 1, 1579.

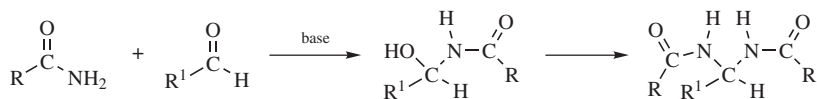
³⁸³See Choudary, B.M.; Jyothi, K.; Madhi, S.; Kantam, M.L. *Synlett* **2004**, 231. For an example in the ionic liquid bmim BF_4 , 1-butyl-3-methylimidazolium tetrafluoroborate, see Yadav, J.S.; Reddy, B.V.S.; Raju, A.K. *Synthesis* **2003**, 883.

³⁸⁴List, B. *J. Am. Chem. Soc.* **2002**, 124, 5656; Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K.A. *J. Am. Chem. Soc.* **2002**, 124, 6254.

OS I, 347, 528, 531; II, 503; III, 328, 501, 717, 723; IV, 603; V, 552; VI, 499; VII, 27.

16-18 Addition of Amides to Aldehydes

Alkylamido-de-oxo-bisubstitution

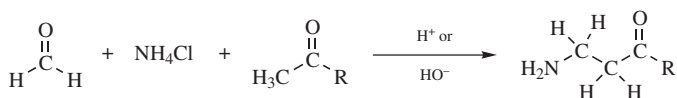


Amides can add to aldehydes in the presence of bases (so the nucleophile is actually RCONH^-) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides.³⁸⁵ If the R' group contains an α hydrogen, water may split out.

Sulfonamides add to aldehydes to give the *N*-sulfonyl imine. Benzaldehyde reacts with TsNH_2 , for example, at 160°C in the presence of $\text{Si}(\text{OEt})_4$,³⁸⁶ with trifluoroacetic anhydride (TFAA) in refluxing dichloromethane,³⁸⁷ or with TiCl_4 in refluxing dichloroethane,³⁸⁸ to give the *N*-tosylimine, $\text{Ts}-\text{N}=\text{CHPh}$. In a similar manner, the reaction of $\text{ToISO}_2\text{Na} + \text{PhSO}_2\text{Na}$ with an aldehyde in aqueous formic acid gives the *N*-phenylsulfonyl imine.³⁸⁹ The reaction of an aldehyde with $\text{Ph}_3\text{P}=\text{NTs}$ and a ruthenium catalyst gives the *N*-tosyl imine.³⁹⁰ Reaction of aldehydes with $\text{LiAl}(\text{NHBn})_4$ also give the corresponding *N*-benzylimine.³⁹¹

16-19 The Mannich Reaction

Acyl,amino-de-oxo-bisubstitution, and so on



In the *Mannich reaction*, formaldehyde (or sometimes another aldehyde) is condensed with ammonia, in the form of its salt, and a compound containing an active hydrogen.³⁹² This can formally be considered as an addition of ammonia to give

³⁸⁵For reviews, see Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 754–759; Zaugg, H.E.; Martin, W.B. *Org. React.* **1965**, *14*, 52, 91–95, 104–112. For a discussion, see Gilbert, E.E. *Synthesis* **1972**, 30.

³⁸⁶Love, B.E.; Raje, P.S.; Williams II, T.C. *Synlett* **1994**, 493.

³⁸⁷Lee, K.Y.; Lee, C.G.; Kim, J.N. *Tetrahedron Lett.* **2003**, *44*, 1231.

³⁸⁸Ram, R.N.; Khan, A.A. *Synth. Commun.* **2001**, *31*, 841.

³⁸⁹Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75.

³⁹⁰Jain, S.L.; Sharma, V.B.; Sain, B. *Tetrahedron Lett.* **2004**, *45*, 4341.

³⁹¹Solladié-Cavallo, A.; Benchebroun, M.; Bonne, F. *Synth. Commun.* **1993**, *23*, 1683.

³⁹²For reviews, see Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791; Gevorgyan, G.A.; Agababyan, A.G.; Mndzhoyan, O.L. *Russ. Chem. Rev.* **1984**, *53*, 561; Tramontini, M. *Synthesis* **1973**, 703; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 654–660. For reviews on the reactions of Mannich Bases, see Tramontini, M.; Angeloni, L. cited above; Gevorgyan, G.A.; Agababyan, A.G.; Mndzhoyan, O.L. *Russ. Chem. Rev.* **1985**, *54*, 495.