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Reductive amination of ketones with ammonia on the surface of an adsorbent

Lyudmila A. Sviridova,[a] Galina A. Golubeva,[a] Alexander N. Tavtorkin,[b] Alexander S. Peregudov[b] and Konstantin A. Kochetkov*[b]

[a] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. Fax: +7 495 932 8846; e-mail: svirid@org.chem.msu.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5085; e-mail: const@ineos.ac.ru*

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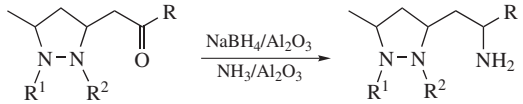
A new mild direct method of amine synthesis *via* the reductive amination of various ketones with ammonia at the surface of an adsorbent was elaborated.

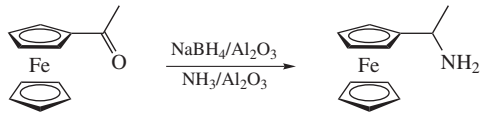
The well-known methods of primary amine synthesis *via* the reductive amination of carbonyl compounds[1,2] require severe conditions, unsuitable for α-(pyrazolidinyl-5/or -3)-alkylketones[3] in view of their low stability. Low solubility of ammonia and ammonium salts in aprotic solvents also prevents the use of sodium triacetoxyborohydride[4] in the reaction. On the other hand, the ability of aluminium oxide to adsorb a significant amount of ammonia and also sodium borohydride on the surface can be used for reduction of carbonyl compounds to alcohols.[5–7] However, such a heterogeneous approach was not applied earlier to a reductive amination of heterocyclic and organometallic carbonyl compounds with ammonia.[8]



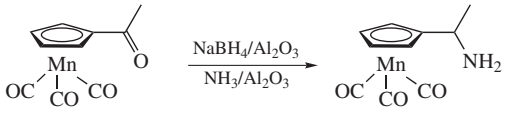
1a,**b**, **3a**,**b** **2a**,**b**, **4a**,**b**

1, **2** R^1 = Ph, R^2 = Ac
3, **4** R^1 = Ac, R^2 = Ph

a R = Me
b R = Ph



5 **6**



7 **8**

We found that the reductive amination of pyrazolidinyl substituted ketones **1a**,**b** or **3a**,**b** with ammonia and sodium borohydride on the surface of aluminium oxide† leads to corresponding primary amines **2a**,**b** or **4a**,**b**‡ in 45–65% yields. The resonances of amines were assigned by a COSY experiment (see Online Supplementary Materials). The dehydrated properties of aluminium oxide have allowed spending reductive amination with fatty aromatic ketones **1b** and **3b**, quite often hardly exposed to reductive amination.[4] The given approach was extended to organometallic ketones **5** and **7**. Under similar conditions acetyl-

† *Preparation of an adsorbent with sprayed sodium borohydride.* In a round-bottom flask, a solution of sodium borohydride (1 g, 26 mmol) in pyridine (25 ml) was added to fresh-baked neutral aluminium oxide (19 g, Reanal), the solvent was removed from the mixture in a vacuum, the residue was washed out with 200 ml of benzene, evaporated and dried in a desiccator over H_2SO_4.

‡ *Procedure for the reductive amination of ketones.* A solution of ketone (0.5 g) in 1 ml CH_2Cl_2 was diluted with 2 ml of hexane and put on fresh-baked neutral aluminium oxide (5 g), the solvent was drived away, the adsorbent was saturated with gaseous ammonia during 1 h and mixed with sodium borohydride applied on aluminium oxide (10 g). A mixture was stirred up without solvent for 48 h on a vibrating multifunctional device,[9] washed out on the filter with diethyl ether (50 ml), the solvent was evaporated, and the rest was dissolved in 5 ml of benzene. Then, 10 ml of water was added for clearing, acidated with H_2SO_4 to pH 6.5, benzene was separated, and the aqueous layer was extracted with benzene (4×5 ml). Then, potassium carbonate (1 g) was added to a water phase and the mixture was extracted with diethyl ether (6×5 ml). Combined ether fractions were dried with anhydrous potassium carbonate and evaporated (TLC on SiO_2 in acetone).

5-(2-Aminopropyl)-1-acetyl-3-methyl-2-phenylpirazolidine **2a**: two diastereomers (~1:1), yield 51%, oil. IR (oil, ν/cm^{-1}): 3303 (NH, ν_s), 3372 (NH, ν_{as}), 1668 (CO). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01, 1.09 (2d, 2×3H, γ-Me, *J* 6.47 and 6.29 Hz), 1.20, 1.22 (2d, 2×3H, 3-Me, *J* 4.86 and 5.21 Hz), 1.30–2.00 (2m, 2×4H, α-CH_2, 4-CH_2), 2.02, 2.05 (2s, 2×3H, MeCO), 2.91, 3.10 (2m, 2×1H, β-H), 4.11 (m, 2H, H-3), 4.55 (m, 2H, H-5), 6.87–7.27 (2×5H, N–Ph). COSY: 1.02 (d, 3H, γ-Me, *J* 6.4 Hz), 1.21 (d, 3H, 3-Me, *J* 6.7 Hz), 1.34 (m, 1H, α-H), 1.82 (m, 1H, H-4), 1.91 (m, 1H, α-H′), 2.00 (m, 1H, H′-4), 2.03 (s, 3H, MeCO), 2.92 (m, 1H, β-H), 4.11 (m, 1H, H-3), 4.55 (m, 1H, H-5), 6.90–7.30 (5H, N–Ph); minor: 1.10 (d, 3H, γ-Me, *J* 6.4 Hz), 1.23 (d, 3H, 3-Me, *J* 6.4 Hz), 1.36 (m, 1H, α-H), 1.56 (m, 1H, α-H′), 1.84 (m, 1H, H-4), 2.00 (m, 1H, H-4′), 2.07 (s, 3H, MeCO), 3.11 (m, 1H, β-H), 4.12 (m, 1H, H-3), 4.60 (m, 1H, H-5), 6.90–7.30 (5H, N–Ph). The elemental analysis was made for phenylthiocarbamoylated derivative of **2a**. Found (%): C, 66.74; H, 7.13; N, 13.78. Calc. for $C_{22}H_{28}N_4OS$ (%): C, 66.63; H, 7.12; N, 14.13.

5-(2-Amino-2-phenylethyl)-1-acetyl-3-methyl-2-phenylpirazolidine **2b**: two diastereomers (~1:1), yield 65%, oil. IR (oil, ν/cm^{-1}): 3297 (NH, ν_s), 3365 (NH, ν_{as}), 1656 (CO). ^{1}H NMR ($CDCl_3$) δ: 1.20, 1.22 (2d, 2×3H, 3-Me, *J* 6.93 and 6.93 Hz), 1.30–2.02 (m, 2×4H, α-CH_2, 4-CH_2), 2.04, 2.12 (2s, 2×3H, MeCO), 3.90–4.19 (2×2H, β-H, H-3), 4.56, 4.64 (m, 2×1H, H-5), 6.78–7.42 (2×10H, Ar). COSY: 1.22 (d, 3H, 3-Me, *J* 6.93 Hz), 1.70 (m, 1H, α-H), 1.81 (m, 1H, α-H′), 1.84 (m, 1H, H-4), 2.00 (m, 1H, H-4′), 2.02 (s, 2H, NH_2), 2.12 (s, 3H, MeCO), 4.13 (dd, 1H, β-H, *J* 9.71 and 4.00 Hz), 4.15 (m, 1H, H-3), 4.64 (m, 1H, H-5), 6.78–7.42 (10H, Ar); minor: 1.20 (d, 3H, 3-Me, *J* 6.93 Hz), 1.67 (m, 1H, α-H), 1.82 (m, 1H, H-4), 2.04 (s, 3H, MeCO), 2.14 (m, 1H, H-4′), 2.39 (m, 1H, α-H′), 3.95 (dd, 1H, β-H, *J* 8.12 and 6.16 Hz), 4.05 (m, 1H, H-3), 4.56 (m, 1H, H-5), 6.78–7.42 (10H, Ar). Found (%): C, 74.31; H, 8.01; N, 12.96. Calc. for $C_{20}H_{25}N_3O$ (%): C, 74.27; H, 7.79; N, 12.99.

ferrocene **5** gives corresponding amine **6**[§] in one stage, whereas two-step synthesis with preliminary precipitation of an oxime and using an excess of sodium as the reducer[5] are required. Under the same conditions from acetylcymantrene **7** labile to light[6] cymantrenylethylamine **8**[¶] was obtained.

Thus, a selective direct method of primary amine synthesis under mild conditions, suitable for conversions of compounds with deactivated carbonyl groups, was developed.

3-(2-Aminopropyl)-1-acetyl-5-methyl-2-phenylpirazolidine **4a**: two diastereomers (~1:1), yield 51%, oil. IR (oil, ν/cm^{-1}): 3303 (NH, ν_s), 3359 (NH, ν_{as}), 1662 (CO). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12, 1.19 (2d, 2×3H, γ-Me, *J* 6.08 and 6.49 Hz), 1.37 (2d, 2×3H, 5-Me, *J* 6.49 and 6.49 Hz), 1.27–1.99 (m, 2×4H, α-CH_2, 4-CH_2), 1.97, 2.00 (2s, 2×3H, MeCO), 3.09 (m, 2H, β-H), 4.00, 4.20 (m, 2H, H-5), 4.36 (m, 2H, H-3), 6.89–7.29 (2×5H, N–Ph). COSY: 1.19 (d, 3H, γ-Me, *J* 6.49 Hz), 1.30 (m, 1H, α-H), 1.37 (d, 3H, 5-Me, *J* 6.49 Hz), 1.55 (m, 1H, α-H'), 1.74 (s, 2H, NH_2), 1.77 (m, 2H, H-4, H-4′), 2.00 (s, 3H, MeCO), 3.09 (m, 1H, β-H), 4.00 (m, 1H, H-5), 4.36 (m, 1H, H-3), 6.89–7.29 (5H, N–Ph); minor: 1.12 (d, 3H, γ-Me, *J* 6.08 Hz), 1.30 (m, 1H, α-H), 1.37 (d, 3H, 5-Me, *J* 6.49 Hz), 1.47 (m, 1H, α-H′), 1.74 (s, 2H, NH_2), 1.77 (m, 1H, H-4), 1.94 (m, 1H, H-4′), 1.97 (s, 3H, MeCO), 3.08 (m, 1H, β-H), 4.20 (m, 1H, H-5), 4.36 (m, 1H, H-3), 6.89–7.29 (5H, N–Ph). The elemental analysis was made for phenylthiocarbamoylated derivative of **4a**. Found (%): C, 66.79; H, 7.09; N, 14.11. Calc. for $C_{22}H_{28}N_4OS$ (%): C, 66.63; H, 7.12; N, 14.13.

3-(2-Amino-2-phenylethyl)-1-acetyl-5-methyl-2-phenylpirazolidine **4b**: two diastereomers (~1:1), yield 62%, oil. IR (oil, ν/cm^{-1}): 3272 (NH, ν_s), 3297 (NH, ν_{as}), 1657 (CO). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37, 1.40 (2d, 2×3H, 5-Me, *J* 6.4 and 6.4 Hz), 1.53–2.04 (m, 2×4H, α-CH_2, 4-CH_2), 2.07, 2.11 (2s, 2×3H, MeCO), 3.79, 4.06, 4.10, 4.30–4.45, 4.50 (2×3H, β-H, H-3, H-5), 6.73–7.40 (2×10H, Ar). COSY: 1.40 (d, 3H, 5-Me, *J* 6.4 Hz), 1.57 (m, 1H, α-H), 1.67–2.04 (3H, α-H′, H-4, H-4′), 2.07 (s, 3H, MeCO), 4.06, (dd, 1H, β-H, *J* 10.3 and 3.4 Hz), 4.37 (m, 2H, H-3, H-5), 6.73–7.40 (10H, Ar); minor: 1.37 (d, 3H, 5-Me, *J* 6.4 Hz), 1.57 (m, 1H, α-H), 1.67–2.04 (4H, α-H, α-H′, H-4, H-4′), 2.11 (s, 3H, MeCO), 4.10, (dd, 1H, β-H, *J* 8.5 and 7.0 Hz), 3.80 (m, 1H, H-3), 4.32 (m, 1H, H-5), 6.73–7.40 (10H, Ar). The elemental analysis was made for phenylthiocarbarmoylated derivative of **4b**. Found (%): C, 70.64; H, 6.61; N, 12.11. Calc. for $C_{27}H_{30}N_4OS$ (%); C, 70.71; H, 6.59; N, 12.22.

[§] *α-Ferrocenylethylamine* **6**: yield 50%, oil. IR (oil, ν/cm^{-1}): 3289 (NH, ν_s), 3365 (NH, ν_{as}). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (d, 3H, CH*Me*, *J* 6.4 Hz), 3.78 (q, 1H, C*H*Me, *J* 6.6 Hz), 4.07–4.16 (9H, Ar). Ref. data[10] (^{1}H NMR, Varian A-60D, $CDCl_3$–D_2O, containing a trace amount of DCl) δ: 1.34 (d, 3H, CH*Me*), 3.84 (q, 1H, C*H*Me), 4.15–4.18 (9H, Ar).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the electronic version at doi:10.1016/j.mencom.2008.09.010.

References

1 V. A. Tarasevich and N. G. Kozlov, *Usp. Khim*., 1999, **68**, 61 (*Russ. Chem. Rev*, 1999, **68**, 55).
2 M. L. Moore, *Org. React*., 1948, **5**, 301.
3 L. A. Sviridova, A. N. Tavtorkin, P. B. Terentiev, I. F. Lescheva, N. G. Kolotyrkina and K. A. Kochetkov, *Khim. Geterotsikl. Soedin*., 2005, 1566 [*Chem. Heterocycl. Compd*. (*Engl. Transl*.), 2005, **41**, 1314].
4 A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Matyanoff and R. D. Shah, *J. Org. Chem*., 1996, **61**, 3849.
5 R. S. Varma and R. K. Saini, *Tetrahedron Lett*., 1997, **38**, 4337.
6 M. Periasamy and M. Thirumalaikumar, *J. Organomet. Chem*., 2000, **609**, 137.
7 E. Santaniello, F. Ponti and A. Manzocchi, *Synthesis*, 1978, 891.
8 R. S. Varma and R. Dahiya, *Tetrahedron*, 1998, **54**, 6293.
9 S. M. Chistovalov and A. N. Chernov, *Kimicheskaya Promyshlennost*, 1997, no. 8, 31 (in Russian).
10 S. Allenmark and A. Grundstrmöm, *Chem. Scr.*, 1973, **4**, 69.
11 N. M. Loim, Z. N. Parnes, V. G. Andrianov, Yu. T. Struchkov and D. N. Kursanov, *J. Organomet. Chem*., 1980, **201**, 301.

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[¶] *α-Cymantrenylethylamine* **8**: yield 45%, oil. IR (oil, ν/cm^{-1}): 3229 (NH, ν_s), 3377 (NH, ν_{as}), 1919, 2016 (CO). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (d, 3H, CH*Me*, *J* 5.0 Hz), 1.42 (s, 2H, NH_2), 3.78 (m, 1H, C*H*Me), 4.60 (s, 1H, C_5H_4), 4.66 (s, 1H, C_5H_4), 4.75 (s, 1H, C_5H_4), 4.84 (s, 1H, C_5H_4). Ref. data[11] (^{1}H NMR, 60 MHz, CCl_4) δ: 1.33 (d, 5H, CH*Me*, NH_2, *J* 5.3 Hz), 3.83 (q, 1H, C*H*Me), 4.69–4.79 (m, 3H, C_5H_4), 4.94 (m, 1H, C_5H_4).