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# An efficient method for the preparation of *N*,*N*-disubstituted 1,2-diamines

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**Abstract**

$C_2$-Symmetric 1,2-diamines are useful precursors to numerous reagents used in asymmetric synthesis and catalysis. We report here an efficient protocol for converting the two most commonly used *trans*-1,2-diamines to *N*,*N*-disubstituted derivatives, a transformation that simplifies the preparation of non-$C_2$-symmetric diamines. Central to the method is the high-yielding conversion of the diamines to the corresponding monoacetylated derivatives via imidazoline intermediates. © 2000 Published by Elsevier Science Ltd.

$C_2$-Symmetric 1,2-diamines are important precursors to chiral reagents for asymmetric synthesis and catalysis.[1] These diamines have seen widest use in the preparation of $C_2$-symmetric chiral auxiliaries, such as those shown in Fig. 1, since differentiating the two nitrogen centers typically requires the use of substoichiometric amounts of a derivatizing agent followed by separation of the resulting mixture of diamine, monofunctionalized diamine and difunctionalized diamine.[2,3] We report here an efficient two-step method for preparing monoacylated derivatives of two common $C_2$-symmetric diamines via imidazoline intermediates (Scheme 1), and show that these monoacylated diamines can be conveniently transformed to *N*,*N*-disubstituted 1,2-diamines (Scheme 2). We anticipate that the convenience of this method will facilitate further exploration of non-$C_2$-symmetric diamine derivatives as chiral auxiliaries and ligands.

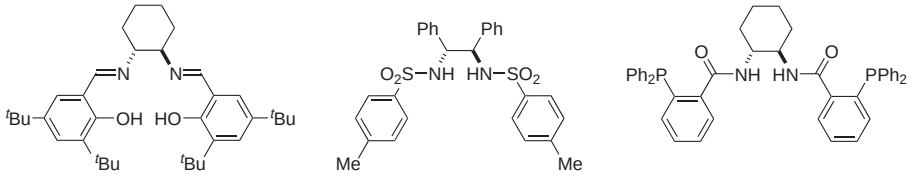


Figure 1.

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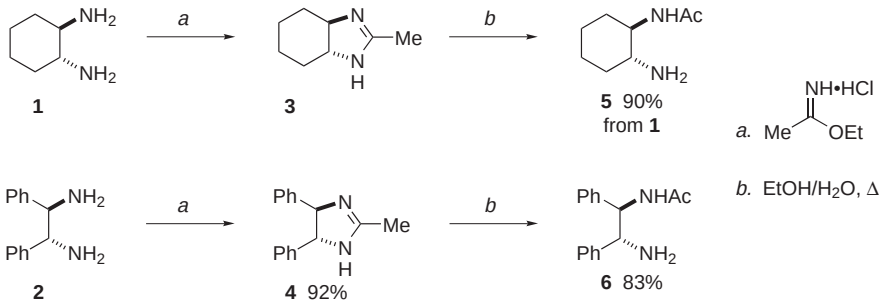
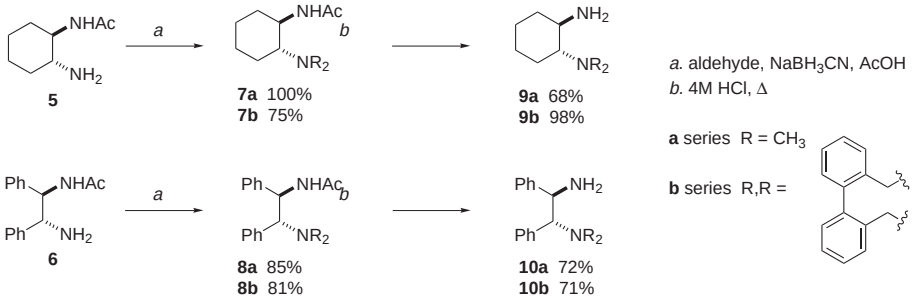



Scheme 1.




Scheme 2.

Condensation of (1*R*,2*R*)-cyclohexane-1,2-diamine (**1**) or (1*S*,2*S*)-1,2-diphenylethylenediamine (**2**) with the Pinner salt derived from acetonitrile conveniently provides the corresponding imidazolines **3** and **4**.[4,5] After evaluating acidic and basic hydrolysis conditions, we have found refluxing a solution of **3** or **4** in neutral ethanol–water mixtures for 12–24 hours to be the best method for effecting conversion to the corresponding monoacetyl diamines **5** and **6**.[6,7]

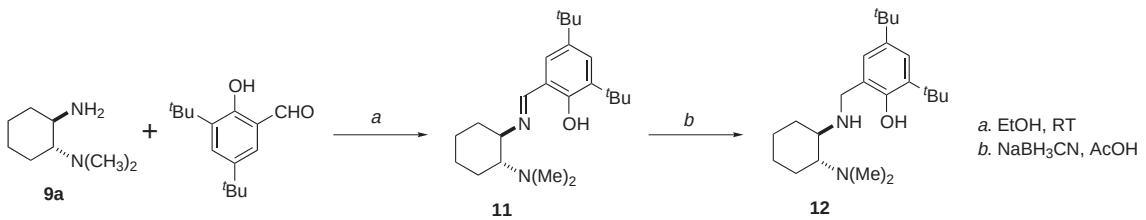
The Pinner salt of benzonitrile also performs acceptably for cyclohexanediamine, providing the corresponding *N*-benzoyl derivative in good yield after hydrolysis of the phenyl imidazoline. However, the phenyl imidazoline prepared from diphenylethylenediamine resisted hydrolysis under all conditions tried. Application of this method to straight-chain diamines such as ethylenediamine led to significantly lower yields (<50%), presumably because oligomerization competes with imidazoline formation.

In a representative procedure, dry acetonitrile (1.0 mL, 19.0 mmol, 2.0 equiv.) was dissolved in dry ethanol (ca. 6 mL). Gaseous HCl was passed through the solution for 1.5 hours, after which residual solvent was removed under a stream of dry $N_2$. The crude imidate hydrochloride, obtained as a white solid, was redissolved in dry ethanol and cooled to 0°C under $N_2$. Cyclohexanediamine (1.1 g, 9.6 mmol, 1 equiv.) was added in one portion and the solution allowed to stir at room temperature for 8–10 hours. 1 M NaOH (aq., 75 mL) was added, and the mixture extracted with 5% $CH_3OH$–$CH_2Cl_2$ (3×50 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated to afford crude **3** (>95% purity by $^1H$ NMR). Compound **3** so obtained (1.3 g, 9.6 mmol) was heated to reflux in 1:1 EtOH–$H_2O$ for 12 hours,[8] whereupon evaporation of the solvent afforded pure **5** (1.4 g, 8.6 mmol) in a 90% yield for two steps.

The monoacetyl diamines can be converted to *N*,*N*-dialkyl derivatives by reductive amination,[9,10] followed by acidic cleavage of the acetamide (Scheme 2). In a typical procedure, **5** (0.6 g, 3.7 mmol, 1 equiv.) and aqueous formaldehyde (37% w/w, 1.5 mL, 18.6 mmol, 5.0 equiv.)

were combined in $CH_3CN$ (20 mL) and stirred for 15 minutes. $NaBH_3CN$ (0.5 g, 7.4 mmol, 2.0 equiv.) was added, followed 15 minutes later by AcOH (1 mL). After 2 hours, the reaction mixture was diluted with 2% $CH_3OH$–$CH_2Cl_2$ (50 mL), washed with 1 M NaOH (3×50 mL), dried over $Na_2SO_4$, and concentrated to afford pure **7a** as a white solid in quantitative yield (0.7 g, 3.7 mmol). Hydrolysis of **7a** to **9a** was effected by refluxing for 12 hours in 4 M HCl. After cooling to ambient temperature, the reaction was made basic by addition of 4 M NaOH (30 mL) and extracted with 5% $CH_3OH$–$CH_2Cl_2$ (3×50 mL). The combined organic fractions were dried over $Na_2SO_4$ and concentrated to afford pure **9a** as a colorless oil (0.4 g, 2.5 mmol, 68%).[11]

In summary, the procedures described provide convenient access to *N*,*N*-disubstituted derivatives of the two most widely-used *trans*-1,2-diamines. This methodology is complementary to that previously developed,[2,3,12] and should prove useful to researchers involved in asymmetric synthesis and catalysis. We have found the diamine derivatives described here to be convenient precursors to tridentate ligands such as **11** and **12** (Scheme 3),[13] which are the focus of ongoing study in our laboratories.




Scheme 3.

## Acknowledgements

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2. For representative examples of diamine monofunctionalization, see: (a) Wennemers, H.; Yoon, S. S.; Still, W. C. *J. Org. Chem.* **1995**, *60*, 1108–1109. (b) Xu, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **1995**, *36*, 7357–7360. (c) Lopez, J.; Liang, S.; Bu, X. R. *Tetrahedron Lett.* **1998**, *39*, 4199–4202. (d) Balsells, J.; Mejorado, L.; Phillips, M.; Ortega, F.; Aguirre, G.; Somanathan, R.; Walsh, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 4135–4142.
3. Solid-phase synthesis has also been used to differentiate symmetrical diamines. See, among others: (a) Fréchet, J. M. *Tetrahedron* **1981**, *37*, 663–683. (b) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327–333.
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6. This is consistent with the currently accepted mechanism of imidate hydrolysis. See: D. G. Nielsen. In *The Chemistry of Amidines and Imidates*; Patai, S.; Rapoport, Z., Eds.; Wiley & Sons: New York, 1991; Vol. 2, Chapter 9.
7. All new compounds were fully characterized by $^{1}H$ and $^{13}C$ NMR, IR, and HRMS. Spectroscopic data for select new compounds: **3**: $^{1}H$ NMR (300 MHz, $CDCl_3$), $\delta$: 4.71 (br s, 1H, NH), 2.77–2.88 (m, 2H, H-2, H-7), 2.03–2.07 (m, 2H, H-6), 1.85 (s, 3H, H-1), 1.66–1.69 (m, 2H, H-3), 1.14–1.38 (m, 4H, H-4, H-5). $^{13}C$ NMR (300 MHz, $CDCl_3$), $\delta$: 165.2, 69.4 (2×C), 30.6, 24.8 (2×C), 16.1 (2×C). FTIR (neat), $cm^{-1}$: 3414(m), 3156(s), 2937(s), 2860(s), 1600(m), 1464(m), 1227(m). HRMS (EI), $m/z$: calcd for $C_8H_{14}N_2$ ($Na^+$): 161.1886, found: 161.1055. **8a**: $^{1}H$ NMR (400 MHz, $CDCl_3$), $\delta$: 7.24–7.29 (m, 6H, H-7–H-9), 7.01–7.09 (m, 4H, H-6, H-10), 6.33 (d, 1H, $J=8.0$ Hz, NH), 5.66 (t, 1H, $J=7.0$ Hz, H-2), 3.51 (d, 1H, $J=7.0$ Hz, H-3), 2.26 (s, 6H, H-4), 1.87 (s, 3H, H-1). $^{13}C$ NMR (400 MHz, $CDCl_3$), $\delta$: 170.4, 141.9, 137.1, 129.9 (2×C), 129.1 (2×C), 129.0, 128.6 (2×C), 128.08 (2×C), 128.0, 76.0, 54.7, 44.6, 24.7. FTIR (neat), $cm^{-1}$: 3283(m), 3033(m), 2784(s), 1648(s), 1549(m), 1217(m), 752(s). HRMS (FAB), $m/z$: calcd for $C_{18}H_{22}N_2O$ ($Na^+$): 305.1630, found: 305.1631. **11**: $^{1}H$ NMR (300 MHz, $CDCl_3$), $\delta$: 8.31 (s, 1H, H-8), 7.35 (d, 1H, $J=2.1$ Hz, H-9), 7.07 (d, 1H, $J=2.4$ Hz, H-10), 3.21 (dt, 1H, $J_1=10$ Hz, $J_2=4.0$ Hz, H-7), 2.60–2.70 (m, 1H, H-2), 2.28 (s, 6H, H-1), 1.60–1.90 (m, 4H, H-3, H-6), 1.44 (s, 9H, H-11), 1.20–1.40 (m, 13H, H-4, H-5, H-12). $^{13}C$ NMR (400 MHz, $CDCl_3$), $\delta$: 165.3, 157.7, 139.9, 136.4, 127.0, 125.8, 117.4, 68.7, 68.0, 40.9, 35.3, 34.9, 34.0, 31.4, 29.33, 25.6, 24.7, 24.1. FTIR (neat), $cm^{-1}$: 2954(s), 2932(s), 2860(m), 2768(w), 1632(m), 1441(m), 1361(w), 1265(w). HRMS (MALDI-FTMS), $m/z$: calcd for $C_{23}H_{38}N_2O$ ($H^+$): 359.3057, found: 359.3061. **12**: $^{1}H$ NMR (300 MHz, $CDCl_3$), $\delta$: 7.22 (d, 1H, $J=2.1$ Hz, H-9), 6.90 (d, 1H, $J=2.4$ Hz, H-10), 4.10 (d, 1H, $J=13$ Hz, H-8), 3.75 (d, 1H, $J=13$ Hz, H-8′), 2.32–2.42 (m, 2H, H-2, H-7), 2.33 (s, 6H, H-1), 1.70–1.85 (m, 4H, H-3, H-6), 1.42 (s, 9H, H-1), 1.18–1.34 (m, 13H, H-4, H-5, H-12). $^{13}C$ NMR (400 MHz, $CDCl_3$), $\delta$: 153.6, 140.7, 135.8, 123.5, 123.1, 122.5, 66.9, 57.4, 49.9, 40.0, 34.9, 34.3, 31.8, 30.9, 29.8, 25.1, 24.6, 21.5. FTIR (neat), $cm^{-1}$: 3274(w), 2951(s), 2934(s), 2861(m), 2829(w), 1599(w), 1480(m), 1458(m), 1238(m), 1103(m). HRMS (MALDI-FTMS), $m/z$: calcd for $C_{23}H_{40}N_2O$ ($H^+$): 361.3213, found: 361.3202.
8. Hydrolysis of the diphenylethylenediamine imidazoline was carried out in 0.5:1:1 dioxane–EtOH–$H_2O$ at 170°C in a sealed tube.
9. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
10. The dialdehyde precursor to the azepine derivatives was prepared by Swern oxidation of the corresponding commercially available diol: Mancuso, A. J.; Swern, D. A. *Synthesis* **1981**, 165–185.
11. Purification of compounds **8a**,**b** and **10a**,**b** required flash column chromatography, employing $CH_3OH$–$CH_2Cl_2$ mixtures as eluent.
12. The procedure described here is, to our knowledge, the most effective for the preparation of these monoacetyl diamines. While Ref. 2a describes the efficient preparation of the monotrifluoroacetamide of *trans*-1,2-diphenylethylenediamine, the lability of trifluoroacyl group limits subsequent transformation.
13. Imine **11** was obtained in 40% yield by combining equimolar amounts of **9a** and 3,5-di-*tert*-butylsalicylaldehyde in $CH_3OH$, removing the solvent under vacuum, and purifying the residue by chromatography with 5% $CH_3OH$–$CH_2Cl_2$. Amine **12** was obtained in 97% yield by reduction of **11** under the conditions described for **7a** ($NaBH_3CN$–AcOH–$CH_3CN$).