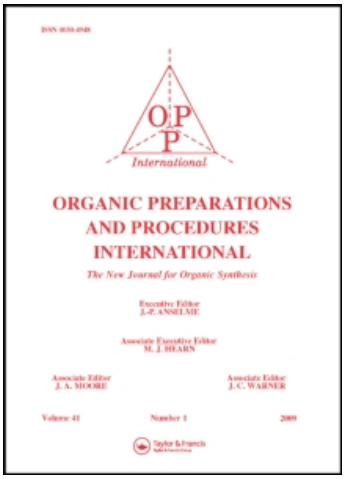

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SYNTHESIS OF 1,3-DIAMINES

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SYNTHESIS OF 1,3-DIAMINES

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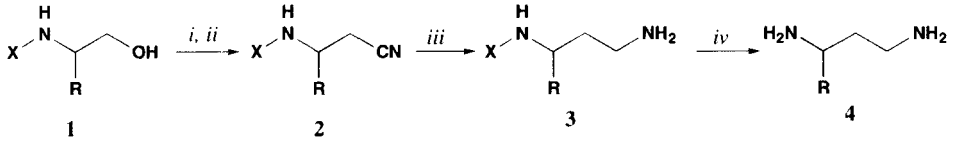
Synthetic routes to diamines are of special interest because these compounds are useful as chelating agents (*cis*-platinum chelates),[1] and as precursors in the synthesis of various interesting medicinal compounds.[2] We recently reported a method for the conversion of amino and peptide alcohols into chiral 1,2-diamines.[3] The existence of only few synthetic approaches to 1,3-diamines,[4,5] prompted us to develop a facile method for the synthesis of 1,3-diamines starting from β-amino alcohols, which are easily derived from natural α-amino acids.[6]



a) X = Boc, R = $C_6H_5CH_2$
b) X = Boc, R = $CH_3CH(CH_3)CH_2$
c) X = Z, R = H

a) R = $CH_3CH(CH_3)CH_2$
b) R = H

i) CH_3SO_2Cl, Et_3N *ii*) NaCN *iii*) $NaBH_4$, $NiCl_2$ *iv*) HCl, THF (or H_2, Pd/C).

The hydroxyl group of *N*-protected-*tert*-butyloxycarbonyl (Boc) or benzyloxycarbonyl (Z)-α-amino alcohols **1a-c** was activated as the mesylates. The methanesulfonates were converted directly into nitriles **2a-c** by treatment with sodium cyanide in *N,N*-dimethylformamide at 60° (3 hrs) in high yield.

Reduction of the nitrile group of **2a-c** may lead to monoprotected 1,3-diamines, **3a-c**. While common reducing agents for the reduction of nitriles to primary amines may be used for Boc-amino nitriles **2a,b**, the benzyloxycarbonyl group of Z-amino nitrile **2c** is converted to *N*-methyl group or cleaved by reagents such as $LiAlH_4$ and catalytic hydrogenolysis. Thus we applied some mild reducing agents for the selective reduction of the cyano group without Z group being affected. Triethylsilane[7] and sodium borohydride in the presence of 10% palladium on charcoal[3] failed to reduce the cyano group. However, the sodium borohydride-transition metal system ($NiCl_2$ or $CoCl_2$)[8] proved to be an excellent selective reducing agent to give N^3-monoprotected 1,3-diamines **3a-c** rapidly (30 min) in high yield. Free 1,3-diamines such as 5-methyl-1,3-diaminohexane (**4a**) and 1,3-diaminopropane (**4b**) were prepared by removal of the protecting groups.

EXPERIMENTAL SECTION

Melting points were measured on a Buchi apparatus and are not corrected. Specific optical rotations were measured with a Perkin-Elmer 141 polarimeter using a 10-cm cell. IR spectra were recorded with a Perkin-Elmer 841 spectrometer. ^{1}H NMR spectra were recorded on a Brucker AC 200 spectrometer at 200 MHz; chemical shifts (δ) are expressed in ppm.

General Procedure for the Synthesis of Nitriles 2a-c.- To an ice-cooled solution of *N*-protected amino alcohol (1 mmol)[6] in dichlororomethane (40 mL), triethylamine (0.21 mL, 1.5 mmol) and methanesulfonyl chloride (0.12 mL, 1.5 mmol) were added together dropwise. The reaction mixture was stirred for 30 min at 0° then 30 min at room temperature. The organic phase was washed consecutively with brine, 1 *M* HCl or 0.5 *M* H_2SO_4, brine, 5% aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude methanesulfonate ester obtained was dissolved in *N,N*-dimethylformamide (2 mL), sodium cyanide (0.12 g, 2.5 mmol) was added and the reaction mixture was heated for 3 hrs at 60°. After cooling, water (12 mL) was added and the precipitated product was collected and dried.

TABLE 1. Physical Constants and Elemental Analyses from **2a-c** to **4a,b**

Cmpd	mp (°C)	$[\alpha]_D^{20}$ (*c*, solvent)	Yields (%)	Elemental Analyses Calcd. (Found) C	H	N
2a	125-126	-19.4° (0.5, $CHCl_3$)	86	68.03[a] (68.31)	7.80 (7.82)	10.58 (10.48)
2b	73- 74	-91.0° (0.5, $CHCl_3$)	82	63.68 (63.69)	9.80 (9.83)	12.38 (12.16)
2c	63- 64		78	64.69 (64.72)	5.92 (6.02)	13.72 (13.68)
3a	oil	-10.8° (1.2, $CHCl_3$)	79	68.15 (68.23)	9.15 (9.18)	10.60 (10.56)
3b	oil	-7.2° (0.7, $CHCl_3$)	74	62.57 (62.61)	11.38 (11.43)	12.16 (12.10)
3c[b]	189-190[c]		71	–	–	–
4a[b]	180-183	-3.8° (0.5, CH_3OH)	92	41.38[d] (41.52)	9.92 (9.89)	13.79 (13.64)
4b[b]	245-247[e]		91	—	—	—

a) Analysis corresponds to $C_{15}H_{20}N_2O_2 \cdot 0.25\ H_2O$. b)As hydrochloride salt. c) Lit.[9] 189.5-190.5°.
d) Analysis corresponds to $C_7H_{18}N_2 \cdot 2\ HCl$. e) Lit.[10] 243°.

TABLE 2. Spectral Data for Compounds **2a-c**, **3a-c** and **4a,b**

Cmpd	IR (cm^{-1})	^1H NMR (δ)[a]
2a	3340 (NH), 2240 (CN), 1690 (OCO)	7.30 (s, 5H, C_6H_5), 4.73 (m, 1H, OCONH), 4.03 (m, 1H, CH), 2.79-3.05 (m, 2H, $CH_2C_6H_5$), 2.39 and 2.68 (dd, J_{gem} = 16Hz, J = 5Hz, 2H, CH_2CN), 1.39 [s, 9H, $C(CH_3)_3$]
2b	3340 (NH), 2240 (CN), 1690 (OCO)	4.59 (m, 1H, OCONH), 3.88 (m, 1H, CH), 2.45 and 2.74 (dd, J_{gem} = 16Hz, J = 5Hz, 2H, CH_2CN), 1.62 [m, 3H, $CH_2CH(CH_3)_2$], 1.42 [s, 9H, $C(CH_3)_3$], 0.89 (m, 6H, $2CH_3$)
2c	3330 (NH), 2250 (CN), 1690 (OCO)	7.32 (s, 5H, C_6H_5), 5.14 (m, 1H, OCONH), 5.08 (s, 2H, 3.45 (m, 2H, CH_2CH_2CN), 2.60 (m, 2H, CH_2CN)
3a	3350 (NH), 1690 (OCO)	7.23 (m, 5H, C_6H_5), 4.68 (m, 1H, OCONH), 3.98 (m, 1H, CH), 2.62-3.05 (m, 4H, CH_2NH_2, $CH_2C_6H_5$), 1.85 (m, 2H, $CHCH_2CH_2$), 1.44 [s, 9H, $C(CH_3)_3$]
3b	3350 (NH), 1690 (OCO)	4.38 (m, 1H, OCONH), 3.72 (m, 1H, CH), 2.55 (m, 1H, CH_2NH_2), 1.35-1.70 [m, 5H, $CH_2CH(CH_3)_2$, $CHCH_2CH_2$], 1.44 [s, 9H, $C(CH_3)_3$], 0.89 (m, 6H, $2CH_3$)
3c	3350 (NH), 1690 (OCO)	7.41 (s, 5H, C_6H_5), 5.12 (s, 2H, $OCOCH_2C_6H_5$), 3.20 (m, 2H, $NHCH_2$), 2.85 (m, 2H, $CH_2NH_3^+$), 1.80 (m, 2H, $CH_2CH_2CH_2$).
4a		3.41 (m, 1H, CH), 3.08 (m, 2H, $CH_2NH_3^+$), 2.00 (m, 2H, $CHCH_2CH_2NH_3^+$), 1.72 [m, 1H, $CH(CH_3)_2$], 1.52 [m, 2H, $CH_2CH(CH_3)_2$], 0.91 (m, 6H, $2xCH_3$).

a) In $CDCl_3$ for **2a-c**, in D_2O for **3a** and **3c**, in CD_3OD for **3b** and **4a**.

General Procedure for the Synthesis of N-Monoprotected Diamines (3a-c).- To a stirred solution of nitrile **2a-c** (1mmol) in methanol (8mL) was added nickel chloride hexahydrate (1.18g, 5 mmol) at 0°, followed by sodium borohydride (0.30g, 8mmol) in small portions. After stirring for 30 min at room temperature, water was added and the mixture neutralized with 0.5 *M* H_2SO_4 and the organic solvent was removed under reduced pressure. The aqueous phase was extracted with ethyl acetate (5x10mL). After drying (Na_2SO_4) the solvent was evaporated to dryness to give the products **3a-c**.

5-Methyl-1,3-diaminohexane (4a).- Compound **3b** (1 mmol) was treated with 4 *M* HCl in THF (12 mL) for 30 min at room temperature. The excess acid and solvents were removed under reduced pressure and the residue reevaporated twice from anhydrous tetrahydrofuran.

1,3-Diaminopropane (4b).- A solution of **3c** (0.5 mmol) in methanol (10 mL) was hydrogenated in the presence of 10% Pd/C for 4h. The catalyst was filtered off and the filtrate was evaporated to dryness.

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A CONVENIENT PREPARATION OF 4-VINYLPHENYLACETIC ACID AND ITS METHYL ESTER

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4-Vinylphenylacetic acid (**1a**) is a potential intermediate for the preparation of a variety of 1,4-disubstituted benzene compounds *via* the differential functionalization of the benzoate ester and olefin groups. The preparations of **1a** and **1b** reported in the literature suffered from several disadvantages; **1a** has been prepared most often by the Friedel-Crafts acetylation of methyl phenylacetate, followed by sodium borohydride reduction and dehydration.[1] The Friedel-Crafts reaction is not regioselective, and the intermediate ketone must be purified by low-temperature crystallization.[2] The only other synthesis of **1a** appears in the patent literature, from 1,4-diethylbenzene in an inconvenient four step process,[3] or from the corresponding nitrile **3**, the preparation of which was not given.[4] We now describe the synthesis of **1b** in three steps and 80-85% overall yield, taking advantage of commercially available, isomerically pure and and reasonably inexpensive ($80/mol) 4-vinylbenzyl chloride (**2**).