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An efficient method for the synthesis of *N*,*N*′-dimethyl-1,2-diamines

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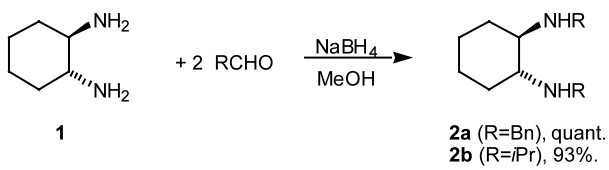
Abstract—A simple method for the preparation of *N*,*N*′-dimethyl-1,2-diamines is described. The method requires the dimethylation of a diazaphospholidine oxide followed by acid-catalysed hydrolysis.

1. Introduction

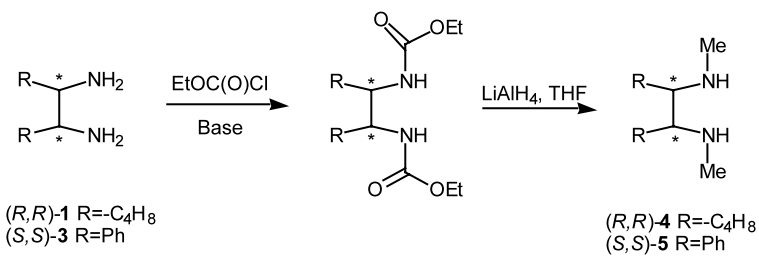
During the course of a project directed towards the synthesis of new ligands for asymmetric catalysis[1] and hosts for the recognition of amino acids,[2] we required a convenient method for the synthesis of a number of *N*,*N*′-dialkylated 1,2-diamines.[3] Particularly desirable were the *N*,*N*′-dimethylated derivatives of enantiomerically pure 1,2-diaminocyclohexane and 1,2-diamino-1,2-diphenylethane, both of which are valuable intermediates for the synthesis of chiral shift reagents,[4] chiral auxiliaries[5] and ligands for use in chiral, non-racemic catalysts.[1,6]



Scheme 1.

In certain cases, we found that *N*,*N*′-dialkylated diamines such as the dibenzyl and di(isopropyl) derivatives **2a**/**b** of (*R*,*R*)-1,2-aminocyclohexane **1** could be simply prepared through the reductive amination of the precursor diamine with a suitable aldehyde or ketone (Scheme 1).

In our initial attempts at *N*,*N*′-dimethylation, however, we found that the situation was rather more complex. Attempted methylation by reductive amination with methanal resulted in the formation of a complex product mixture, presumably due to a polyalkylation process. Attempted dimethylation of (*S*,*S*)-*trans*-1,2-diphenylethylene diamine **3** and (*R*,*R*)-*trans*-1,2-diaminocyclohexane **1** has been described by Alexakis, and involves the formation of a bis carbamate followed by lithium aluminium hydride reduction (Scheme 2).[4] However, this failed to give reproducible results in our hands. Consistent problems of incomplete reduction leading to formation of a highly insoluble, cyclic urea prompted a search for an alternative route to these compounds.



Scheme 2.

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An attractive alternative route to **4** and **5** was to first protect both amines through the use of a 'bridging' group which could then be removed after *N*-methylation. The choice of protecting group, however, would be crucial for success; a very stable group (such as a urea) might prove too difficult to remove after methylation, whilst a very labile one might not survive the methylation conditions. Previous work in our group[7] and by others[8] suggested that a phenyl diazaphospholidine intermediate would be ideal for this application. The formation of such compounds is well established and, whilst they are highly stable to basic conditions, their hydrolysis may be achieved under mildly acidic conditions.

In the event, reaction of diamines (*R*,*R*)-**1** and (*S*,*S*)-**3** with phenyl phosphonic dichloride in the presence of an excess of triethylamine resulted in the efficient formation of phenyl diazaphospholidine oxides **6** and **7**. Bis-methylation of each was achieved using *n*-BuLi in THF at 0°C, to generate the bis anions, followed by quenching with methyl iodide at 0–20°C to give **8** and **9** in 100 and 96% yield respectively. The methylated phenyl diazaphospholidine oxides **8** and **9** were then hydrolysed in refluxing HCl–methanol to give the corresponding, highly crystalline, diamine hydrochloride salts which were recrystallised from isopropyl alcohol to remove the phosphate ester side products. The pure hydrochloride salts were then converted, by washing with saturated potassium carbonate solution, to the free diamines (*R*,*R*)-**4** and (*S*,*S*)-**5** in 66 and 84% yields, respectively (Scheme 3).

2. Conclusion

In conclusion, we have demonstrated that the use of diazaphospholidine protecting group for 1,2-diamines greatly facilitates the preparation of *N*,*N*′-disubstituted derivatives. Although the process requires three steps in contrast to the two step process of carbamate formation/reduction, the yields of each step are high and the processes involved at each stage are accessible to any laboratory with an interest in this area.

3. Experimental

3.1. (*R*,*R*)-*N*,*N*′-Dibenzyl-1,2-diaminocyclohexane 2a[6a]

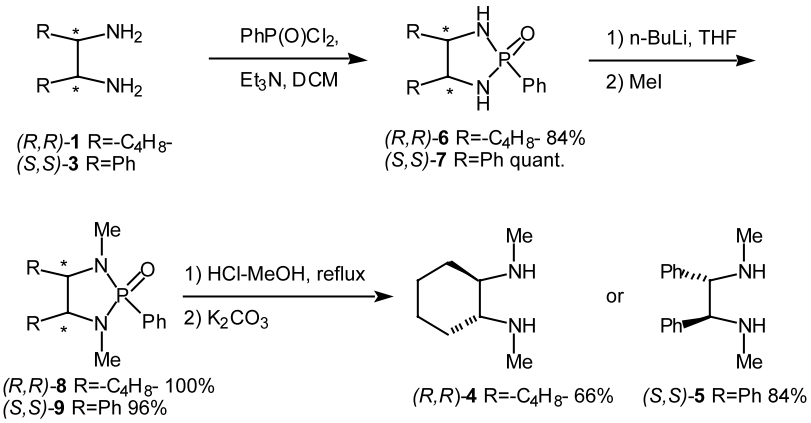
(*R*,*R*)-1,2-Diaminocyclohexane **1** (1.0 g, 8.77 mmol) was dissolved in anhydrous MeOH (5.0 mL) and heated to reflux. Benzaldehyde (1.78 mL, 17.54 mmol) was added dropwise over a period of 2 min and the mixture stirred at reflux for 30 min. The solution was allowed to cool to room temperature and sodium borohydride (700 mg, 18.4 mmol) was added portionwise. After the vigorous effervescence had subsided the mixture was heated to reflux for 15 min. The reaction was then quenched by the addition of water (5 mL) and the aqueous phase extracted with DCM (3×10 mL). The separated organics were dried over potassium carbonate, filtered and the solvent evaporated to give the diamine **2a** as a waxy solid (2.60 g, 100%); $[\alpha]_D^{20} = -80.0$ (*c* 2.5, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 7.40–7.15 (10H, m), 3.90 (2H, d, $J = 13.1$), 3.65 (2H, d, $J = 13.1$), 2.30–2.10 (4H, m), 1.87 (2H, bs, NH), 1.81–1.60 (2H, m), 1.30–0.90 (4H, m).

3.2. (*R*,*R*)-*N*,*N*′-Diisopropyl-1,2-diaminocyclohexane 2b[4a]

(*R*,*R*)-1,2-Diaminocyclohexane **1** (1.0 g, 8.77 mmol) was dissolved in EtOH (30.0 mL) and acetone (3.21 mL, 43.85 mmol) was added. The mixture was then subjected to atmospheric hydrogenation in the presence of platinum oxide (Adam's catalyst) (50 mg). After stirring for 24 h the catalyst was removed by filtration through a plug of Celite and the solvent removed under reduced pressure to give the diamine **2b** as a colourless oil (1.62 g, 93%); $[\alpha]_D^{20} = -120$ (*c* 2.5, $CHCl_3$) [cf. lit.[4a] $[\alpha]_D^{20} = -125.2$ (*c* 9.64, $CHCl_3$)]; δ_H (250 MHz, $CDCl_3$) 2.94–2.79 (2H, m), 2.20–2.00 (4H, m), 1.75–1.60 (2H, m), 1.28–1.15 (2H, m), 1.10–0.85 (16H, m); *m*/*z* (thermospray) 199 (MH+, 90%).

3.3. (R_{3a},R_{7a})-2-Phenyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-1,3,2-benzodiazaphosphole 2-oxide 6

(*R*,*R*)-(−)-1,2-Diaminocyclohexane **1** (400 mg, 3.51 mmol) was dissolved in DCM (20.0 mL) and triethyl-



Scheme 3.

amine (1.0 mL, 7.0 mmol) was added and the mixture cooled to 0°C. Phenyl phosphinic dichloride (0.51 mL, 3.51 mmol) was added slowly dropwise. After 30 min the mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of water and the separated organics were dried over sodium sulfate, filtered and the solvent evaporated to give **6** as a pale yellow solid (696 mg, 84%); mp 186–188°C; $[\alpha]_D^{20}=+4.3$ (*c* 0.51, methanol); (found: C, 60.6; H, 7.4; N, 11.6. $C_{12}H_{17}N_2OP$ requires: C, 61.02; H, 7.20; N, 11.86%); ν_{max} 3215, 1312, 1201, 1183, 1108, 1075, 951, 897 and 744 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.92–7.87 (2H, m), 7.51–7.40 (3H, m), 3.30 (1H, m), 3.08–3.02 (1H, m), 2.96 (1H, d, $J=12.2$), 2.86 (1H, d, $J=5.9$), 1.95 (1H, m), 1.85 (1H, m), 1.81 (2H, m), 1.56–1.35 (4H, m); δ_C (68 MHz, CD_3OD) 26.2 (t), 26.8 (dt, $J_{PC}=4.4$), 34.8 (t), 36.2 (t), 57.1 (dd, $J_{PC}=5.5$), 59.1 (dd, $J_{PC}=18$), 129.8, 129.9, 130.0, 130.1, 132.6, 132.8, 132.9, 133.6; δ_P (162 MHz, $CDCl_3$) 25.8; *m*/*z* 236 (M+, 100%), 194 (7), 101 (77), 86 (47); (found [M]+, 236.1037. $C_{12}H_{17}N_2OP$ requires *m*/*z*, 236.1078).

3.4. (R_{3a},R_{7a})-1,3-(Dimethyl)-2-phenyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-1,3,2-benzodiazaphosphole 2-oxide 8

Compound **6** (1.0 g, 4.24 mmol) was dissolved in THF (20.0 mL) and cooled to 0°C. *n*-BuLi (3.4 mL, 8.53 mmol of 2.5 M solution in hexanes) was added dropwise. The resulting orange solution was stirred for 1 h before dropwise addition of methyl iodide (0.53 mL, 8.52 mmol). After 1.5 h at room temperature the reaction was quenched by the addition of water and the aqueous extracted with DCM (3×20 mL). The combined organics were dried over sodium sulfate, filtered and solvent evaporated to give **8** as a white solid (1.15 g, 100%); $[\alpha]_D^{20}=-29.5$ (*c* 0.9, $CHCl_3$); ν_{max} ($CHCl_3$ film) 1441 (P–Ar), 1250 (P=O) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.80–7.72 (2H, m), 7.54–7.41 (3H, m), 2.97–2.89 (1H, m), 2.66–2.53 (4H, m), 2.28 (3H, d, $J=11.2$), 2.12 (1H, m), 2.01–1.98 (1H, m), 1.88–1.85 (4H, m), 1.39–1.21 (4H, m); δ_C (100 MHz, $CDCl_3$) 132.7 (CH), 131.5 (CH), 130.0 (C*i*), 128.3 (CH), 65.5 (CH), 63.7 (CH), 28.8 (CH_3), 28.3 (CH_2), 24.4 (CH_2); δ_P (160 MHz, $CDCl_3$) 34.1 (s); *m*/*z* (CI) 265 (MH+, 100%); (found: 265.146084. $C_{14}H_{21}N_2OP$ requires MH, 265.146977).

3.5. (*R*,*R*)-*N*,*N*′-Dimethyl-1,2-diaminocyclohexane 4[4a]

Compound **8** (2.56 g, 9.70 mmol) was dissolved in methanol (20.0 mL) and to this was added 0.8 M HCl/methanol (20.0 mL) and the mixture stirred at reflux for 24 h. The pale yellow solution was cooled to room temperature and the solvent evaporated to give a brown solid. Crystallisation from IPA gave the diamine hydrochloride salt as a white crystalline solid. The salt was dissolved in saturated potassium carbonate solution and extracted into DCM (3×30 mL). The organics were dried over potassium carbonate, filtered and solvent evaporated to give diamine **4** as a white, waxy solid (910 mg, 66%); $[\alpha]_D^{20}=-140.2$ (*c* 4.05, $CHCl_3$) [cf. lit.[4a] $[\alpha]_D^{20}=-145.7$ (*c* 4.47, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 2.39 (6H, s), 2.12–2.01 (4H, m), 1.74–1.65 (4H, m), 1.28–1.16 (2H, m), 0.99–0.94 (2H, m).

3.6. (*S*,*S*)-*N*,*N*′-Dimethyl-1,2-diphenylethylenediamine 5[3f]

(S_3,S_4)-1-Phenyl-(3,4-diphenyl)diazaphospholidine 1-oxide **7** was prepared from **3** in the same way as reported for **6** in quantitative yield; δ_H (270 MHz, $CDCl_3$) 8.11–8.04 (2H, m), 7.54 (3H, s), 7.29 (7H, s), 7.20 (3H, s), 4.69 (1H, d, $J=8.8$), 4.53 (1H, d, $J=8.8$), 3.30 (1H, d, 15.4), 3.24 (1H, d, $J=9.0$). Compound **7** was then converted into (S_3,S_4)-1-phenyl-*N*,*N*′-dimethyl-(3,4-diphenyl)diazaphospholidine 1-oxide **9** using the method described for **8** in 96% yield; δ_H (270 MHz, $CDCl_3$) 8.03–7.95 (2H, m), 7.64–7.53 (3H, m), 7.33–7.10 (10H, m), 4.25 (1H, d, $J=8.8$), 4.10 (1H, d, $J=8.6$), 2.44 (3H, d, $J=10.6$), 2.20 (3H, d, $J=9.9$). Finally **5** was prepared from **9** as described for **4** in 84% yield; $[\alpha]_D^{20}=-18.0$ (*c* 0.155, $CHCl_3$) [cf. lit.[3f] $[\alpha]_D^{20}=-18.0$ (*c* 1.0, $CHCl_3$)]; δ_H (270 MHz, $CDCl_3$) 7.16–7.09 (6H, m), 7.05–7.02 (4H, m), 3.57 (2H, s), 2.47 (2H, bs), 2.26 (6H, s).

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