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AN EFFICIENT SYNTHESIS OF N,N'-SUBSTITUTED SYMMETRICAL DIAMINES.

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Abstract: N,N'-substituted symmetrical diamines are readily prepared in high yields in a one-pot procedure from diazidoalcanes and dichloroboranes. This approach has been extended to the synthesis of thermine, a tetramine isolated from *Thermus Thermophilus*.

Diamines are of current interest due to the biological activity of some of their derivatives ¹, their role in metal chelation ² and their potential as starting material in heterocyclic chemistry ³. A great deal of attention has also been focused on tetramines which are involved in differenciation and proliferation processes ⁴. In the last few years, considerable effort has been devoted to the syntheses of these compounds ⁵. We recently reported new approaches for the preparation of polyamines based on the reaction of azide with dichloroborane ⁶.



Table. Synthesis of N,N'-substituted diamines 1

Products	R	n	R'	m.p.(°C)	Yield(%)
1a	Н	2	C ₆ H ₅	198-200	74
1 b	Н	2	C ₆ H ₁₃	235-237	80
1 c	Н	3	C ₆ H ₅	255	85
ld	Н	3	C ₆ H ₁₃	255-257	65
1 e	Н	4	C ₆ H ₅	200	73
11	CH ₃	2	C ₆ H ₁₃	a	68ª

^a If was isolated as a free base, b.p. = $80-85^{\circ}C/0.01$ mm Hg (bulb to bulb distillation)

This secondary amine synthesis proceeds with good chemioselectivity and prevents the formation of any polyalkylation products usually observed, for example, in the reaction of amines with alkyl halides ⁷.

We now wish to report a convenient procedure to prepare N,N'substituted symmetrical diamines 1 from diazides 2 (scheme A).

Readily available starting materials 2 and 3 are combined to give diamines 1 with high yields (Table). No sophisticated purification steps are necessary



Scheme B

since a simple filtration gives pure hydrochlorides 1. The very efficient phenylation reaction at nitrogen is also worthy of note.

This approach can easily be extended to the synthesis of symmetrical tetramines. For example, thermine tetrahydrochloride 6, 4 HCl ⁸ was prepared according to a similar sequence, where a γ -bromodichloroborane 4 was used as a precursor of a γ -aminopropyl chain (scheme B).

All the compounds are characterized by ¹H, ¹³C NMR, elementary analysis or mass spectrometry.

In conclusion, the present method offers distinct advantages over previously reported procedures. There is no contamination by polyalkylated products and therefore no tedious purification, starting materials are readily available and good yields are obtained.

EXPERIMENTAL SECTION

The ¹H and ¹³C NMR spectra were recorded on a Brucker AS300 spectrometer using deuteriochloroform or D_2O (dihydrochlorides) as solvent. Glassware were thoroughly oven-dried and cooled under nitrogen prior to use. Diazidoalcanes was prepared from dihalogenoalcanes ⁹ and dichloroboranes

from alkenes according to the litterature procedures ¹⁰. Toluche was distilled over sodium and benzophenone and stored under nitrogen.

General Procedure : A solution of diazidoalcane (5 mmol.) in 5 mL of toluene is added dropwise over 15 mn to an ice-cooled solution of 11 mmol of dichloroborane in 5 mL of toluene. Nitrogen evolution starts almost immediatly. After 12 hr at room temperature, 1 ml of MeOH is slowly added. The solution is stirred for an additional 10 mn, then 10mL of ether is added and the precipitate isolated by filtration. Recristallization from acetonitrile/methanol gives pure diamines 1 as their dihydrochlorides.

N,N'-(diphenyl)-1,3-diaminopropane dihydrochloride, **1a**, 2HCl. m.p. = 198-200°C. Yd = 74 %. ¹H NMR, δ : 1.95 - 2.30 (m, 2H), 3.33 - 3.55 (m, 4H), 7.20 - 7.55 (m, 10H). ¹³C NMR, δ : 24.5, 50.8, 125.2, 132.7, 133.4, 137.2. Anal. for C₁₅H₂₆N₂, 2HCl calc. C, 58.44 ; H, 6.81 ; N, 9.36. Found : C, 58.4 ; H, 6.7 ; N, 9.1.

N,N'-(dihexyl)-1,3-diaminopropane dihydrochloride, **1b**, 2HCl. m.p. = 235-7°C. Yd = 80 %. ¹H NMR, δ : 0.72 - 1.00 (m, 6H), 1.15 - 2.30 (m, 18H), 2.92 - 3.25 (m, 8H). ¹³C NMR, δ : 16.0, 24.4, 25.4, 28.0, 28.2, 33.1, 47.1, 50.7. Anal. for C₁₅H₃₄N₂, 2HCl calc. C, 57.13 ; H, 11.51 ; N, 8.88. Found : C, 56.9 ; H, 11.6 ; N, 8.9.

N,N'-(diphenyl)-1,4-diaminobutane dihydrochloride, 1c, 2HCl. m.p. = 255°C. Yd = 85 %. ¹H NMR, δ : 1.58 - 1.83 (m, 4H), 3.25 - 3.55 (m, 4H), 7.25 - 7.55 (m, 10H). ¹³C NMR, δ : 25.0, 53.5, 125.3, 132.7, 133.3, 137.1.

Anal. for C₁₆H₂₀N₂, 2HCl calc. C, 61.35 ; H, 7.08 ; N, 8.94. Found : C, 61.3 ; H, 7.1 ; N, 8.9.

N,N'-dihexyl-1.4-diaminobutane dihydrochloride, **1d**, 2HCl. m.p. = 255-257°C. Yd = 73 %. ¹H NMR, δ : 0.87 - 1.12 (m, 6H), 1.25 - 2.05 (m, 20H), 3.05 - 3.37 (m, 8H). ¹³C NMR, δ : 16.0, 24.4, 25.5, 28.1, 28.2, 33.2, 49.6, 50.6. Anal. for C₁₆H₃₆N₂, 2HCl calc. C, 58.34 ; H, 11.63 ; N, 8.50. Found : C, 58.1 ; H, 11.9 ; N, 8.9.

N,N'-diphenyl-1,5-diaminopropane dihydrochloride, **1e**, 2HCl. m.p. = 200°C. Yd = 93 %. ¹H NMR, δ : 1.50 - 2.12 (m, 6H), 3.40 - 3.70 (m, 4H), 7.45 - 7.75 (m, 10H). ¹³C NMR, δ : 25.4, 27.3, 54.0, 125.3, 132.7, 133.2, 137.9. Anal. for C₁₇H₂₂N₂ calc. C, 62.39 ; H, 7.39 ; N, 8.56. Found : C, 62.3 ; H, 7.4 ; N, 8.6.

N,N'-dihexyl-1-méthyl-1,3-diaminopropane **1f**. b.p. = 80 - 85°C/0.01 mm Hg. Yd = 68 %. ¹H NMR, d : 0.70 - 1.75 (m, 28H), 1.03 (d, J = 6.2 Hz, 3H), 2.40 - 2.87 (m, 7H). ¹³C NMR, d : 14.0, 20.6, 22.7, 27.1, 27.2, 30.1, 30.4, 31.8, 37.2, 47.4, 47.6, 50.2, 52.5. Mass spectrum, exact mass calc. for $C_{16}H_{36}N_2$: M⁺ m/z 256.287, found 256.287.

Synthesis of thermine tetrahydrochloride, 6, 4HCl.

N,N'-di-(3-bromopropyl)-1,3-diaminopropane dihydrochloride, **5**, 2HCl was prepared according to the general procedure. m.p. > 260°C. Yd = 66 %. ¹H NMR, δ : 2.00 - 2.50 (m, 6H) ; 3.05 - 3.37 (m, 8H) ; 3.58 (t, J = 6.2 Hz, 4H). ¹³C NMR, δ : 25.3, 31.1, 32.4, 47.4, 49.3. Anal. for C9H₂₀Br₂N₂, 2 HCl : calc. C, 27.76 ; H, 5.65 ; N, 7.19. Found : C, 27.9 ; H, 5.5 ; N, 7.0. N,N'-di-(3-azidopropyl)-1,3-diaminopropane. To a solution of 680 mg (1.75 mmol) of **5**, 2HCl in 5 mL of water are added with stirring 560 mg (8.5 mmol) of NaN₃. The reaction mixture is heated (90-95°C, oil bath) with stirring for 12 h. Water is removed under reduced pressure. 1 mL of 50 % KOH was added followed by 10 mL of ether. The organic phase is separated and the diamine is extracted again from the aqueous phase with 3 x 10 ml of ether. The combined organic extracts are dried (K₂CO₃) and the solvent is removed under vacuum. The crude oil thus obtained is of sufficient purity and is used as such in the next step. Yd = 82 %. ¹H NMR, δ : 1.55 - 1.95 (m, 8H) ; 2.58 - 2.83 (m, 8H) ; 3.38 (t, J = 6.4 Hz, 4H). ¹³C NMR, δ : 29.4, 30.3, 47.0, 48.5, 49.7. Mass spectrum, exact mass calc. for C₉H₂₀N₄ (M-2N₂)⁺ : m/z 184.169 ; found : 184.169.

Thermine tetrahydrochloride 6, 4HCl. A solution of the diazide (1.5 mmol) in ethanol (5 mL) and HCl 12N (1 ml) is hydrogenated over 10 % palladium on charcoal (50 mg) at 60 psi of hydrogen in a parr apparatus for 18 h at room temperature. The catalyst is separated by filtration and the solvent evaporated under reduced pressure. The solid thus obtained is collected by filtration and is washed with ethanol. F > 260°C. Yd = 89 %. ¹H NMR, δ : 1.87 - 2.37 (m, 6H) ; 3.03 - 3.35 (m, 8H). ¹³C NMR, δ : 25.4, 26.6, 39.5, 47.4, 47.6. Anal. for C9H₂₄N₄, 4 HCl calc. C, 32.34 ; H, 8.38 ; N, 16.76. Found : C, 32.3 ; H, 8.3 ; N, 17.0.

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