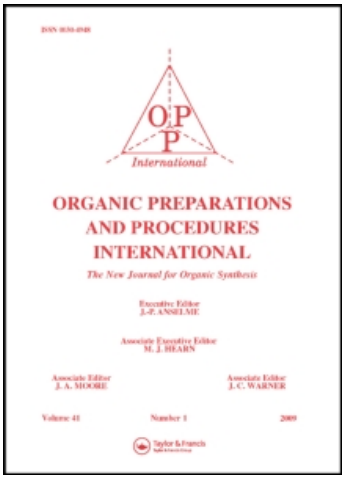

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A SAFE AND CONVENIENT PROCEDURE FOR THE SYNTHESIS OF POLYAMBSES *via* AZIDE INTERMEDIATES

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Ethyl 3-Ethenyl-2(ethoxycarbonyloxy)indole-1-carboxylates (2). General Procedure.- To a solution of **1** (10 mmol) in CH_2Cl_2 (50 mL) was added ethyl chloroformate (2.9 mL, 30 mmol). After cooling at 0-5° triethylamine (5.6 mL, 40 mmol)in CH_2Cl_2 (15 mL) was added under stirring. After allowed to warmed up to room temperature overnight, the reaction mixture was washed with H_2O (2 x 50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The products were purified by column chromatography on silica gel and crystallized (Table 1).

REFERENCES

1. E. M. Beccalli and A. Marchesini, *Synth. Commun.*, **23**, 2945 (1993).

2. R. J. Sundberg, *"The Chemistry of Indoles"*, Academic Press, New York, NY, 341 (1970).

3. E. M. Beccalli, A. Marchesini and T. Pilati, *Synthesis*, 891 (**1992**).

4. A. Windaus, H. Jensen and A. Schramme, *Ber.*, **57**, 1875 (1924).

5. G. N. Walker, R. T. Smith and B. N. Weaver, *J. Med. Chem.*, **8**, 626 (1965).

6. A. Wahl and V. Livovschi, *Bull. Soc. Chim. France*, **5**, 653 (1938).

7. P. L. Julian, H. C. Printy, R. Ketcham and R. Doone, *J. Am. Chem. Soc.*, **75**, 5305 (1953).

8. W. Ziegenbein and W. Franke, *Chem. Ber.*, **90**, 2291 (1957).

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A SAFE AND CONVENIENT PROCEDURE FOR THE SYNTHESIS OF POLYAMINES *via* AZIDE INTERMEDIATES

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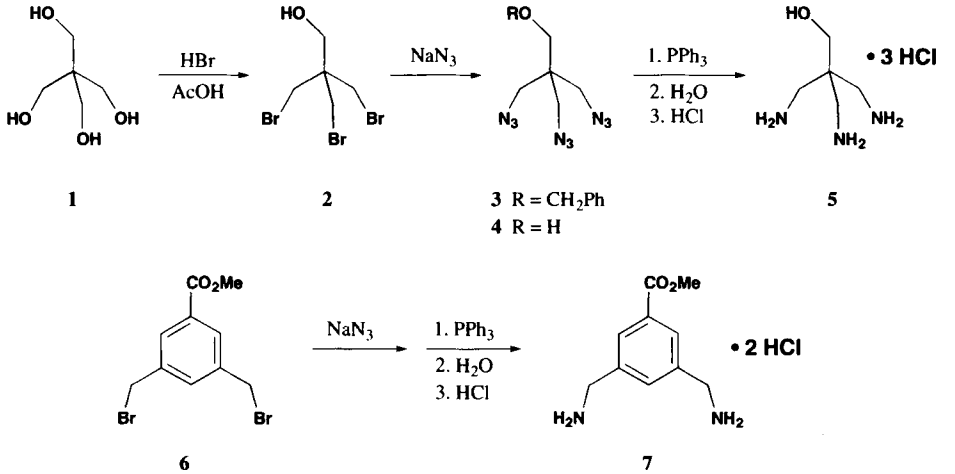
In connection with our studies on molecular amplifiers for contrast enhancement in magnetic resonance imaging (MRI),[1] we required a safe, efficient synthesis of several functionalized polyamines including triamine **5** and diamine **7**. Triamine **5** has exhibited interesting chelation properties[2] and synthetic potential.[3] Procedures for the preparation of **5** from pentaerythritol (**1**) involve discrimination among four equivalent hydroxyl groups and introduction of the amino groups. In one recent synthesis,[4] the requisite discrimination was achieved by initial formation of a bicyclic

orthoester derivative involving three of the four hydroxy groups. After protection of the remaining hydroxyl group through benzylation, the orthoester was hydrolyzed and the amino groups were introduced by way of formation of triazide intermediate **3**. Catalytic hydrogenation of the azido groups and deprotection afforded the target triamine **5**. Disadvantages of this elegant method are the protection-deprotection sequence and the isolation of the potentially explosive triazide intermediate **3**. Herein, we wish to report an improved synthesis of triamine **5** and similar preparation of diamine **7**.

Tribromide **2** was easily prepared by treatment of pentaerythritol (**1**) with HBr.[5] Direct amination of **2** with ammonia was complicated by the formation of an oxetane intermediate, ring opening of which by ammonia required harsh conditions.[6] We have found that substitution of all three bromine atoms by excess azide ion under relatively mild conditions may be accomplished. In order to avoid the explosion hazard of pentaerythritol–derived polyazides,[4] the triazide intermediate **4** was converted into triamine **5** in solution without isolation by reaction with triphenylphosphine followed by *in situ* hydrolysis of the intermediate iminophosphorane.[7] We employed an analogous reaction sequence for the preparation of methyl 1,3-*bis*(aminomethyl)benzoate (**7**) from dibromo ester **6**.



The R–Br → R–NH_2 procedure herein reported was used for the preparation of a variety of polyamines on a 3–5 g scale. Overall yields were reproducible and were similar to those described here. The product amines were sufficiently pure for use for the next reaction.

EXPERIMENTAL SECTION

Melting points were obtained in a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Nicolet Magna-IR 550 IR FT spectrometer. ^1H (300 MHz) and ^{13}C (75 MHz) were taken on a GE QE-300 FT NMR spectrometer.

3-Amino-2,2-*bis*(aminomethyl)-1-propanol (5).- A mixture of tribromide **2**[5] (6.48 g, 20 mmol) and NaN_3 (15.6 g, 240 mmol) in DMF (120 mL) was stirred under N_2 at 100 ° for 16 hrs. Then it was cooled to room temperature, poured into H_2O (1 L) and extracted with ether (200 mL + 4 x 75 mL).

The extract was dried over $MgSO_4$ and concentrated to about 100 mL. Dioxane (200 mL) was added and the mixture was again concentrated to 100 mL. Additional dioxane (150 mL) was added with stirring followed by triphenylphosphine (26.2 g, 100 mmol) and aqueous ammonia (100 mL). The mixture was stirred for 20 hrs and evaporated to dryness. The residue was suspended in $CHCl_3$ (400 mL) and extracted with 2N HCl (5 x 75 mL). The extract was washed with $CHCl_3$ (4 x 20 mL, discarded) and concentrated to about 30 mL. Concentrated HCl (10 mL) was added and the acidic mixture was kept for 20 hrs at 4°. The precipitated colorless crystals were collected, washed with cold concentrated HCl (3 mL), ethanol (3 mL), ether (5 x 20 mL) and dried *in vacuo* to afford 2.81 g (58%) of triamine trihydrochloride **5**, mp. 295-297° (dec.) (from conc. HCl); lit.[9] 298° (dec), pure by NMR[8] and reverse-phase TLC.

Methyl 3,5-*bis*(Aminomethyl)benzoate Dihydrochloride (7).- A mixture of methyl 3,5-*bis*(bromomethyl)benzoate (**6**)[10] (3.72 g, 11.6 mmol) and NaN_3 (3.00 g, 46 mmol) in acetone (100 mL) and H_2O (10 mL) was refluxed for 4 hrs, then cooled to room temperature and poured into H_2O (500 mL). The mixture was extracted with ether (100 + 4 x 25 mL) and the extract was dried over $MgSO_4$ and concentrated on a rotary evaporator in a 0.3 L flask to about 50 mL. Dry THF (200 mL) was added and the mixture was again concentrated to 50 mL. More THF (200 mL) was added to the stirred solution, followed by triphenylphosphine (8.82 g, 39 mmol) (vigorous evolution of gas observed). After 6 hrs stirring, H_2O (6.5 mL, 40 mmoL) was added and the mixture was stirred for 16 hrs. The solvent was removed on a rotary evaporator and the residue was suspended in $CHCl_3$ (200 mL) and extracted with 2N HCl (8 x 30 mL). The acidic extract was washed with $CHCl_3$ (5 x 20 mL, discarded) and evaporated. The solid residue was dissolved in boiling methanol (50 mL). The hot solution was filtered and the filtrate was cooled to room temperature. The product was precipitated by addition of dry ether (about 250 mL) to yield 2.58 g (67%) of diamine dihydrochloride **7**[11] as a white powder, mp. 264-266° (from methanol). ^1H NMR (D_2O): δ 3.85 (s, 3H), 4.20 (s, 4H), 7.67 (s, 1H), 8.03 (s, 2H). ^{13}C NMR (D_2O): δ 42.75, 53.32, 130.63, 131.70, 134.37, 134.50, 146.19, 168.24. IR (KBr): 3412, 3150-2800, 2680-2600, 1713, 1563, 1527, 1314, 1232, 1127, 969, 914, 776 cm^{-1}.

Anal. Calcd. for $C_{10}H_{16}Cl_2N_2O_2$: C, 44.96; H, 6.04; N, 10.49. Found: C, 44.92; H, 6.11; N, 10.34

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REFERENCES

1. J. F. W. Keana, L. Lex, J. S. Mann, J. M. May, J. H. Park, S. Pou, V. S. Prabhu, G. M. Rosen, B. J. Sweetman and Y. Wu, *Pure Appl. Chem.*, **62**, 201 (1990).

2. M. A. Green, M. J. Welch and J. C. Huffman, *J. Am. Chem. Soc.*, **106**, 3689 (1984).

3. G. H. Searle and R. J. Geue, *Australian J. Chem.*, **36**, 927 (1983).

4. T. J. Dunn, W. L. Neumann, M. M. Rogic and S. R. Woulfe, *J. Org. Chem.*, **55**, 6368 (1990).

5. A. I. Dyachenko and M. Y. Lukina, *Izv. Akad. Nauk. SSSR Ser. Khim.*, 2237 (**1966**); *CA*, **66**, 75713f (1967).

6. M. Beyaert and F. Govaert, *Proc. Roy. Acad. Sci. Amsterdam*, **37**, 156 (1934).

7. H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).

8. Chemical shifts corresponded to reported values (ref. 4).

9. A. Litherland and F. G. Mann, *J. Chem. Soc.*, 1588 (**1938**).

10. H. A. Staab and R. G. H. Kirrstetter, *Ann.*, 886 (**1979**).

11. At this point the compound was 98% pure by HPLC [Rainin Microsorb C18 4.6 x 250 mm column, eluent-gradient (0.1% TFA in MECN) in (0.1% TFA in H_2O) from 10% to 75% in 20 min; UV detection at 220 and 254 nm], t_r = 10.1 min.

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IMPROVED PREPARATION OF 2,5-DIMETHYL-1,4-CYCLOHEXANEDIONE

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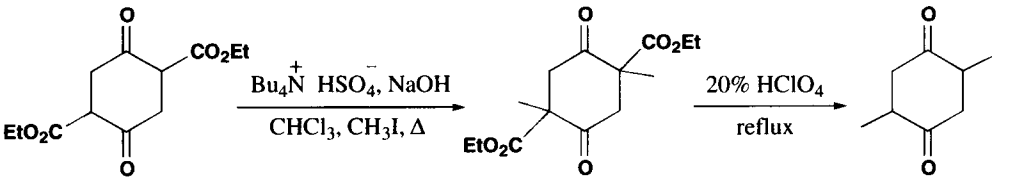
Dione **1**, a very useful compound in synthetic organic chemistry, was needed in our group for the preparation of oxotetrahydrocarbazoles by the Fischer indole synthesis. While the compound has been reported in the literature,[1] the experimental conditions are not reproducible. The problem in its synthesis lies in the dialkylation of diester **2**.[2] Several methods have been attempted but the yields were poor (*e. g. t*-BuOK/DMSO, MeI) or the methods were not reproducible (*e. g.* NaH/DMF, MeI).



2 **3** **1**

Based on the monomethylation of cyclic β-oxophosphonates using phase-transfer catalysis,[3] we attempted the same procedure on compound **2** for its dimethylation. The phase-transfer reagent, tetrabutylammonium hydroxide, was generated *in situ* from tetrabutylammonium hydrogen sulfate