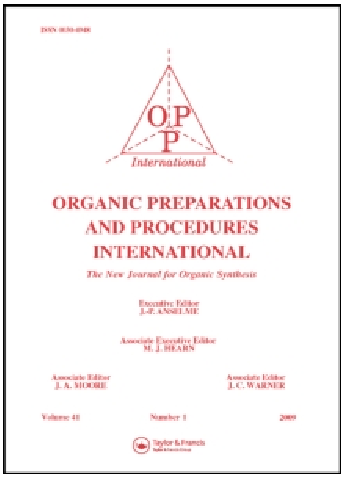

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2,4-BIS(BROMOMETHYL)-5-METHYL-N-ACETYL BENZYLAMINE AND 2,4-BIS(CYANOMETHYL)-5-METHYL-N-ACETYLBENZYLAMINE

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2,4-BIS(BROMOMETHYL)-5-METHYL-N-ACETYL BENZYLAMINE

AND

2,4-BIS(CYANOMETHYL)-5-METHYL-N-ACETYLBENZYLAMINE

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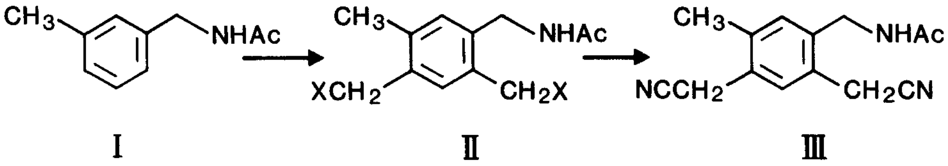
2,4-Bis(cyanomethyl)-5-methyl-N-acetylbenzylamine (III) has been an important intermediate for the synthesis of cyclopenta[f]isoquinoline derivatives, a new class of compounds which bind to DNA.[1-3] The reported[1] synthesis of III involves the use of chloromethyl methyl ether (carcinogen) and is thus not suitable to large scale synthesis.



a) X = Br b) X = Cl

Olah and coworkers[4] have described 1,4-bis(chloromethoxy)butane and 1,4-bis(bromomethoxy)butane as halomethylating agents. Initial attempts to chloromethylate I with 1,4-bis(chloromethoxy)butane under Olah's condition, did not succeed. However, the use of anhydrous $AlCl_3$ in dichloromethane afforded compound IIb in a satisfactory yield. The corresponding bromo-compound (IIa) was obtained in better yield by using 1,4-bis(bromomethoxy)-butane as an alkylating agent. 2,4-Bis(bromomethyl)-5-methyl-N-acetyl-benzylamine (IIa) was converted to 2,4-bis(cyanomethyl)-5-methyl-N-acetyl-benzylamine (III) with sodium cyanide in dimethylformamide. The reactions proceed in high yield and are adaptable to large scale synthesis.

EXPERIMENTAL

Mps. were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The IR spectra were obtained on a Beckman 4210 in a fluorinated hydrocarbon. PMR spectra were recorded on a Varian EM-390 90-MHz NMR spectrometer using tetramethylsilane as internal reference. Mass spectra were taken on a Hewlett-Packard, Model 5985 spectrophotometer.

2,4-Bis(bromomethyl)-5-methyl-N-acetylbenzylamine (IIa). - A mixture of m-methyl-N-acetylbenzylamine[1] (40g, 0.25 mol) and 1,4-bis (bromomethoxy) butane[4,5] (640g, 2.32 mol) in dichloromethane (1000 ml) was cooled in an ice bath. To the cooled solution, anhydrous aluminum chloride (140g, 1.1 mol) was added portionwise. An orange brown color appeared during addition of aluminum chloride. After the addition of aluminum chloride was completed, the mixture was further stirred in the ice bath for another hour and then refluxed for 40 hours. The mixture was then cooled to room temperature and poured slowly into an ice-hydrochloric acid (10%) mixture; a slightly greenish white solid precipitated. The solid was filtered, air-dried and dried under vacuum over phosphorus pentoxide to yield a white solid (74g, 84%), mp. 194-199°. It was crystallized from acetone to give a white solid (62 g, 72%), mp. 208-209° (dec.); NMR: (DMSO-d_6): 1.9 (s, 3H, $C\underline{H}_3CO$), 2.32 (s, 3H, $C\underline{H}_3Ar$), 4.32 (d, 2H, J = 6Hz, $-C\underline{H}_2N$), 4.68 (s, 2H, $-C\underline{H}_2-$), 4.72 (s, 2H, $-C\underline{H}_2-$), 7.12 (s, 1H, Ar-$\underline{H}$), 7.48 (s, 1H, Ar-$\underline{H}$) and 8.4 (broad, 1H, N$\underline{H}$-).

Anal. Calcd. for $C_{12}H_{15}NOBr_2$: C, 41.26; H, 4.30; N, 4.01; Br, 45.85

Found: C, 41.10; H, 4.22; N, 3.85; Br, 46.20

2,4-Bis(chloromethyl)-5-methyl-N-acetyl benzylamine (IIb). - Compound (IIb) could be obtained from m-methyl-N-acetylbenzylamine (7.8 g, 0.05 mol), 1,4-bis(chloromethoxy)butane[4,5] (90 g, 0.48 mol) dissolved in dichloromethane (250 ml) and anhydrous aluminum chloride (32 g, 0.24 mol). The reaction was carried out as for compound IIa. Compound IIa was obtained in 54% yield, and was crystallized from acetone to 6.0 g (46%) of a white solid, mp. 173-174° (lit.[1] 174-176°), identical from IR, NMR and MS comparisons with a sample made by using chloromethyl methyl ether as an alkylating agent.[1]

2,4-Bis (cyanomethyl)-5-methyl-N-acetylbenzylamine (III), mp. 143-144°, was obtained in 97% yield from IIa as described for IIb.[1,6]

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4. G. A. Olah, D. A. Beal, S. H. Yu, and J. A. Olah, Synthesis, 560 (1974); G. A. Olah, D. A. Beal and J. A. Olah, 41, 1624 (1976).
5. All reactions should be carried out in a good hood because of the potential toxic nature of the alkylating agents and their decomposition products.
6. The material was identical with an authentic sample made according to reference 1 from IR, NMR and MS comparisons. Crude IIa could be used for the above reaction giving somewhat lower yields (75-85%).

PHOTOCHEMICAL SYNTHESIS OF BULLVALENEDIONE[†]

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The synthesis of a novel fluxional compound, bullvalenedione IV is of interest, since IV can be directly converted to its semidione which is presumed to serve as a potential intermediate for the intriguing rearra-