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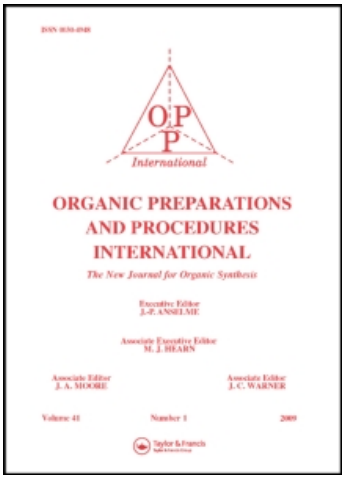

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FACILE SYNTHESIS OF 2-METHOXYISOBUTYLISONITRILE

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then filtered and the residue washed with methylene chloride. The filtrate was washed successively with water (3x20 ml), aq. sodium carbonate (5%, 3x20 ml) and dried (Na_2SO_4). This methylene chloride solution was treated with triethylamine (5.05 g, 0.05 mol) at 20° and stirred for 1 hr. It was then washed with water (2x25 ml), dil. HCl (2%, 2x25 ml) followed by water (3x20 ml) and dried (Na_2SO_4). Removal of solvent by distillation under reduced pressure (see note on safety above) furnished the diazoacetate 3 (3.82 g, 90% based on prenyl alcohol). IR: 2120, 1710, 1240 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 1.73 (s, 6H), 4.53 (d, J = 7 Hz, 2H), 4.56 (s, 1H), 5.26 (m, 1H).

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FACILE SYNTHESIS OF 2-METHOXYISOBUTYLISONITRILE

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2-Methoxyisobutylisonitrile is a key starting material for the preparation of Tc-99m hexakis (2-methoxyisobutylisonitrile) which appears to be clinically useful as a myocardial perfusion agent.[1] The synthesis of a number of isocyanides have been reported.[2] A new synthetic route to isocyanides which utilizes trichloromethyl chloroformate ("diphosgene") as a dehydrating agent has been reported recently.[3] We now report a procedure for the preparation of 2-methoxyisobutylisonitrile in a 26% overall yield from commercially available 2-hydroxyisobutyronitrile in only four steps. While our work was in progress, two independent syntheses were reported,[4,5] one involving six steps (no yields were reported)[4] and the applied for patent requiring a five-step process[5] with an overall yield of 8.1%.

Etherification of nitrile 1 was effected with anhydrous methanol and freshly fused zinc chloride to give ether 2 (51%), which was successfully reduced with lithium aluminum hydride to give 3 in good yield (82%) in about 8 hrs. N-Formylation of 3 with ethyl formate in the

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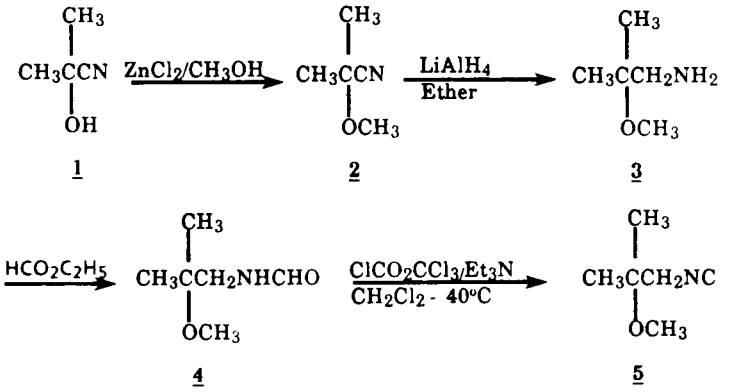
presence of a catalytic amount of p-toluenesulphonic acid readily gave the amide 4. Treatment of



1 2 3 4 5

4 with trichloromethyl chloroformate ("diphosgene") at -40° in the presence of triethylamine in methylene chloride afforded 5 as a colorless liquid in 67% yield. Mass spectral, ^{1}H and ^{13}C NMR analyses support the structures. The compound could be stored in a refrigerator for six months.

EXPERIMENTAL SECTION

^{1}H-NMR and ^{13}C-NMR spectra were recorded in ppm downfield from Me_4Si on 270 MHz JEOL-FX 270 spectrophotometer in $CDCl_3$. Mass spectra were determined on a Finnigan TSQ spectrometer. 2-Hydroxyisobutyronitrile (Aldrich) and ethyl formate were obtained commercially and used without further purification. The diphosgene (Fluka) was used as received.

CAUTION: Isonitriles should be prepared in a hood since they are toxic and vile-smelling liquids.

2-Methoxyisobutyronitrile (2).- To a solution of freshly fused zinc chloride (149 g, 1.09 mol) in anhydrous methanol (100 mL) was added 2-hydroxyisobutyronitrile (100 mL, 93 g, 1.09 mol). The mixture was heated (60°) in an oil bath for 12 hrs. After cooling to room temperature, the reaction mixture was poured onto ice. It was then extracted with ether (3x200 mL) and the combined extracts dried (Na_2SO_4). Removal of the solvent and distillation of the residue afforded 55.2 g (51%) of 2-methoxyisobutyronitrile, bp. 117-118°, lit.[6] bp. 117°.

^{1}H NMR ($CDCl_3$): δ 1.31 (s, 6H, $(CH_3)_2C$), 3.25 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 26.23 (CH_3-), 53.12 (OCH_3), 71.12 (-C-), 120.28 (CN).

2-Methoxyisobutylamine (3).- To a well stirred slurry of lithium aluminum hydride (9.0 g, 0.24 mol) in dry ether (500 mL) was added dropwise a solution of 2-methoxyisobutyronitrile (19.8 g, 0.20 mol) in dry ether (150 mL). The mixture was stirred under reflux for 8 hrs. Excess hydride was carefully destroyed by the dropwise addition of water. The mixture was filtered and the filter cake washed with ether (6x150 mL). The combined ethereal solution was dried (Na_2SO_4). After removal of ether, the residual liquid was distilled to give 16.8 g (82%) of 3, bp. 124-125°.

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Anal. Calcd for $C_5H_{13}NO$: C, 58.21; H, 12.70; N, 13.58
Found: C, 58.17; H, 12.84; N, 13.74

^1H NMR ($CDCl_3$): δ 1.16 (s, 6H, $(CH_3)_2C$), 1.6 (s, 2H, NH_2), 2.65 (s, 2H, CH_2), 3.26 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 22.31 (CH_3), 49.15 (CH_2), 50.38 (OCH_3), 74.77 (C). MS: m/e 104 (M+1).

N-Formyl-2-methoxyisobutylamine (4).- To a stirred solution of 2-methoxyisobutylamine 3 (16.4 g, 0.16 mol) and a catalytic amount of p-toluenesulphonic acid (75 mg) at 0° was slowly added ethyl formate (11.79 g, 12.92 mL, 0.16 mol). After the slightly exothermic reaction ceased, the solution was refluxed for 16 hrs, and the product was distilled through a Vigreux column to give 19.36 g (93%) of N-formyl-2-methoxyisobutylamine 4, bp. 74°/15 mm.

Anal. Calcd for $C_6H_{13}NO_2 \cdot 1H_2O$: C, 54.08; H, 10.01; N, 10.51
Found: C, 53.90; H, 9.85; N, 10.59

^1H NMR ($CDCl_3$): δ 1.13 (s, 6H, $(CH_3)_2C$), 3.15 (s, 3H, OCH_3), 3.27 (d, J = 5.8 Hz, 2H, CH_2) 6.0 (bs, 1H, NH), 8.19 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 22.65 (CH_3), 46.26 (CH_2), 49.60 (OCH_3), 161.53 (CHO). MS: m/e 132 (M+1).

2-Methoxyisobutylisonitrile (5).- To a cooled (-40°) solution of N-formyl-2-methoxyisobutylamine (9.0 g, 0.69 mol) and triethylamine (19.5 mL, 14.16 g, 0.14 mol) in dry dichloromethane (100 mL) was added dropwise trichloromethyl chloroformate ("diphosgene") (4.15 mL, 6.8 g, 0.035 mol) in dry dichloromethane (50 mL) over a period of 1 hr. After the addition was complete, the temperature of the reaction was allowed to rise to 0° and the mixture was stirred for 1 hr, and at reflux temperature for 0.5 hr. Water (25 mL) was added and the organic layer separated. The organic layer was washed with a saturated solution of sodium bicarbonate (25 mL), water (25 mL) and dried (Na_2SO_4). Evaporation of the methylene chloride left a dark brown liquid. The dark brown liquid obtained was distilled under vacuum to give 5.2 g (67%) of the isonitrile 5 as a colorless liquid, bp. 60-61°/22 mm.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.72; H, 9.89; N, 12.70

^1H NMR ($CDCl_3$): δ 1.25 (s, 6H, $CH_3)_2C$), 3.22 (s, 3H, OCH_3), 3.38 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 22.23 (CH_3), 49.69 (OCH_3), 50.32 (CH_2), 73.06 (C), 157.49 (NC). MS: m/e 114 (M+1).

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AN IMPROVED SYNTHESIS OF 2-ISOCYANATOBENZONITRILE

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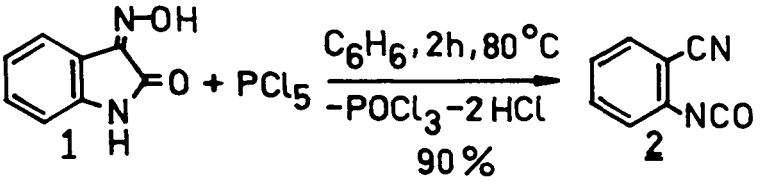
2-Isocyanatobenzonitrile, a useful reagent for the synthesis of ureas[1] and heterocycles,[2] can be prepared by dehydration and rearrangement[3] of isatin oxime. However, all literature procedures have serious disadvantages. In our hands, the use of diethyl ether in the method of Borsche et al.[4] was quite unsuitable as reaction medium because both isatin oxime and phosphorus pentachloride are nearly insoluble in it; as a result, the reaction is slow and a number of distillations of the crude product are necessary. An attempt to overcome these difficulties by



the use of excess phosphorus oxychloride led to another hazardous and inconvenient work-up procedure involving numerous distillations.[5] We now describe a convenient procedure for a modified synthesis of 2-isocyanatobenzonitrile.

The use of a solution of phosphorus pentachloride in dry benzene or toluene insured a clean and rapid reaction, especially since isatin oxime is sufficiently soluble as well. After the reaction ceases, simple extraction without distillation afforded 2-isocyanatobenzonitrile (2) in high yield.[6]