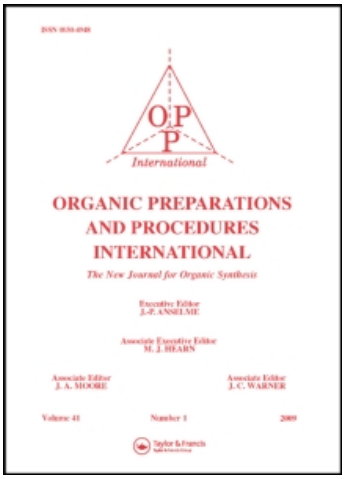

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EFFICIENT SYNTHESIS OF 4-ISOCYANO-2,2,6,6-TETRAMETHYLPIPERIDINE-1-OXYL

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EFFICIENT SYNTHESIS OF 4-ISOCYANO-2,2,6,6-TETRAMETHYLPIPERIDINE-1-OXYL

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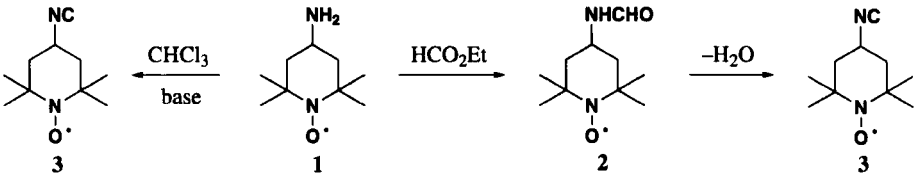
Isocyanides have a wide range of synthetic potential[1-5] as starting compounds for the multicomponent reactions (MCRs) such as the Passerini and Ugi reactions, which are powerful tools for the creation of combinatorial libraries.[3,4,6-8] Isocyanides are also versatile building blocks for the synthesis of heterocycles.[5,8,9] Aryl, benzyl, cyclohexyl and *t*-butyl isocyanides[3,6] (the last three are commercially available) are most commonly used in these reactions. Herein we report an efficient and high yield synthesis of 4-isocyano-2,2,6,6-tetramethylpiperidine-1-oxyl. This compound will enrich the set of available isocyanides and allow the insertion of a spin label fragment into MCRs products, libraries created in MCRs reactions and heterocycles built from isocyanides.

The two most important routes to isocyanides involve the dehydration of *N*-substituted formamides using phosgene, phosphorus oxychloride, thionyl chloride or other dehydrating systems,[1,3] and by the reaction of primary amines with chloroform in the presence of strong bases.[1,10] Both routes have been reported for the synthesis of the title isocyanide **3**. The reaction of the amine **1** with chloroform[11,12] in the presence of solid potassium hydroxide gave **3** in only 9% yield,[11] while the dehydration of the formamide **2** with $POCl_3$/pyridine reagent in petroleum ether is reported to afford a 67% yield of **3**.[13]



We examined both methods[11,13] and found that the reaction of amine **1** with chloroform, 50% sodium hydroxide and a PTC catalyst (BTEACl) gave **3** in 16% yield (instead 9%[11]). In our hands, several experiments involving the dehydration of **2** with $POCl_3$/pyridine system gave very low (28-33%), albeit reproducible yields instead of 67% as previously reported.[13] We also applied some other reagents such as $POCl_3/NEt_3$,[14] $SOCl_2$/DMF,[1b,c,15] phenyl chlorothionoformate,[16] used for the dehydration of formamides with no satisfactory results, the yields being 13%, 0% and 0%, respectively.

Much better results were obtained when phosgene in the presence of triethylamine[1a] (the classical dehydration agent) was used. Ice-bath temperature, control of the excess of phosgene solution in CH_2Cl_2(about 150 mol%), close control of both consumption of the amide **2** and formation of the isocyanide **3** (TLC) ensure an excellent yield (84%) of the desired product **3**.

EXPERIMENTAL SECTION

Melting points (uncorrected) were recorded using a hot stage microscope. TLC was performed on silica gel with 254 nm fluorescent: Merck 5554, 5562. Visualization: UV 254 nm and I_2 vapours. Column chromatography was done on silica gel < 0.08 mm (Merck 7729), 60 G for TLC (Merck 7731), Serva for TLC (27185), Merck 1.09385.1000. MS (EI, 70 eV, m/e, int.[%]), IR (ν [cm^{-1}], KBr) and EPR (a_N [G]) data were recorded using AMD M-40, FT/IR Jasco 420, and Bruker ESP 300 E apparatus, respectively. 4-Amine-2,2,6,6-tetramethylpiperidine-1-oxyl **1** was prepared according to the literature method.[17] All commercially available chemicals were used as received.

4-Formamido-2,2,6,6-tetramethylpiperidine-1-oxyl (2).- 4-Amino-2,2,6,6-tetramethylpiperidine-1-oxyl (**1**, 6.71 g, 39.2 mmol), was refluxed with a large excess of ethyl formate (100 mL) for 5 h. The formation of **2** was monitored by means of TLC (silica, benzene:methanol 9:1, 3:1). Excess ethyl formate was evaporated under the reduced pressure (rotary evaporator, water aspirator). The crude red crystalline residue (7.8 g, 100%, mp. 90-98°C) may be used for the next step. Column chromatography (silica, benzene:methanol 95:5, 9:1) gave pure **2** (7.47 g, 96%, m.p. 102-103°C). In order to obtain an analytical sample, pure **2** (~250 mg) was placed in a Soxhlet extractor and leached with hexane (~70 mL) for 3 h. Filtration of orange crystals from cooled hexane solution gave an analytical sample of **2** (75 mg), mp. 104-106°C, *lit.*[13] 105-106°C. MS (EI, 70 eV): 199 (24, M), 185 (7), 169 (10), 154 (38), 140 (14), 139 (28), 124 (96), 113 (100), 109 (89), 98 (87), 84 (15), 70 (21), 68 (54); IR (KBr): 3471, 3232, 1680 cm^{-1}.

Phosgene Solution.- ***Caution**: All operations with gaseous phosgene and its methylene chloride solution must be performed in an efficient ventilated hood.* Methylene chloride (20 mL) was saturated with phosgene up to about 20% volume increase. The concentration of phosgene was determined iodometrically.[18] To a mixture of the solid potassium iodide (5 g) and acetone (30 mL) chilled in a refrigerator, the phosgene solution in methylene chloride (v = 0.5 to 1 mL) was added. The mixture was shaken for about 3 min and iodine was titrated with sodium thiosulfate (N = 0.1 n, V [mL]). Concentration of phosgene [mol/L] = (N x V)/(2 x v).

4-Isocyano-2,2,6,6-tetramethylpiperidine-1-oxyl (3).- To a magnetically stirred solution of **2** (1.99 g, 10 mmol), triethylamine (2.55 g, 25.2 mmol, 3.5 mL), and methylene chloride (10 mL) cooled in an ice bath, a solution of phosgene in methylene chloride was added dropwise from a burette at 5-8°C. The formation of **3** was monitored using TLC (silica, benzene:methanol 9:1). About 150-165 mol% (~6 mL) of the phosgene solution was required for completion of the reaction. A stream of gaseous ammonia was passed through the reaction mixture at < 20°C to destroy excess phosgene, and methylene chloride was evaporated under the reduced pressure (rotary evaporator, water aspirator). Benzene (15-20 mL) was then added, and the mixture was stirred vigorously and filtered (to remove urea, triethylamine hydrochloride and ammonium chloride). The filtrate was concentrated under the reduced pressure (rotary evaporator, water aspirator), and the solid, red residue was subjected to column chromatography (silica, benzene:methanol 95:5) to give 1.52 g **3** (84%), mp. 142-144°C (hexane), *lit.*[11,13]: 133-134°C, 143.5-144.5°C.

MS (EI, 70 eV): 181 (31, M), 167 (18), 166 (11), 151 (10), 140 (8), 136 (10), 126 (9), 124 (24), 109 (35), 94 (100), 81 (36), 69 (40), 68 (74), 67 (67), 57 (23), 56 (38), 55 (52), 53 (33), 41 (98), 39 (40); IR (KBr): 2143 cm^{-1}; EPR (a_N): 15.49 G (toluene), 15.77 G (dichloromethane), 15.83 G (DMSO), g = 2.0060.

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