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CONVENIENT SYNTHESIS OF 2-THIONAPHTHYLMETHYL ISOCYANIDE : A USEFUL REAGENT FOR METHYL ISOCYANIDE TRANSFER

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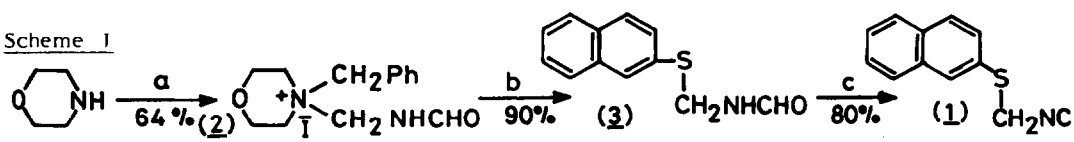
ABSTRACT : The crystalline 2-thionaphthylmethyl isocyanide (1), prepared from the novel N-(formamidomethyl)-N-benzyl morpholinium iodide (2), via transfer of elements of CH_2NHCHO, is totally devoid of pervasive odour. The cyclo-addition of the conjugate base of (1) to nitriles followed by desulfurization, under very mild conditions, provides an attractive route to imidazoles.

The cyclo-addition of arylthiomethyl isocyanide conjugate bases to nitriles constitutes an attractive route to imidazoles.[1] During endeavours to use this reaction for transformations in the peptide domain, we realized a major shortcoming of either $PhSCH_2NC$ or $p\text{-}CH_3C_6H_4SCH_2NC$. They were noxious and evil smelling liquids.[2] The present communication reports on a satisfactory solution to this problem and endeavours to recommend the use of 2-thionaphthylmethyl isocyanide (1) for such cyclo-addition reactions.

The preparation of (1) envisaged the transfer of a formamidomethyl unit from (2) to 2-thionaphthol.[3] The reagent (2), mp 156°C[4], was prepared from morpholine in an overall yield of 64%[5] and the transfer to 2-thionaphthol achieved in 90% yields. The resulting 2-thionaphthylmethyl formamide (3), mp 63°C, was converted to (1), mp 75°C in 80% yields (Scheme I).[6] The most attractive feature of (1) is the absence of the highly disagreeable and pervasive odour associated with the earlier isocyanides and, in our opinion, the procedure for (1) reported here[7] from the overall view point of yields, simplicity, convenience of work-up[6].

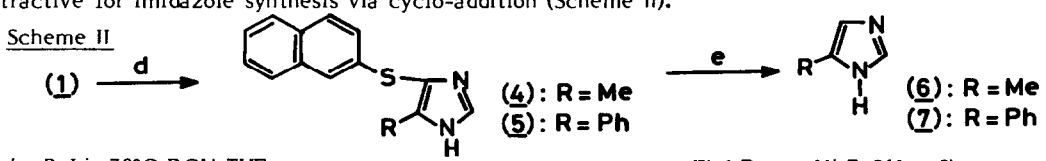
Scheme I



a.i. formalin, $HCONH_2$ ii. $PhCH_2I,CHCl_3$ b.2-thionaphthol,Et_3N,PhH c.PPh_3,CCl_4,Et_3N,$CHCl_3$

The efficacy of (1) for the transfer of elements of CH_3NC has been established, via cyclo-addition of the conjugate base, generated with n-BuLi at -78°C, to CH_3CN and PhCN, leading to respectively, 4-thionaphthyl-5-methyl imidazole (4) and 4-thionaphthyl-5-phenyl imidazole (5), in 95% and 64% yields.[8] Compounds (4) and (5) were desulfurized to 4(5)-methyl imidazole (6,73%) and 4(5)-phenyl imidazole (7,56%).[1,9] We feel that the methodology presented here is the most attractive for imidazole synthesis via cyclo-addition (Scheme II).[10]

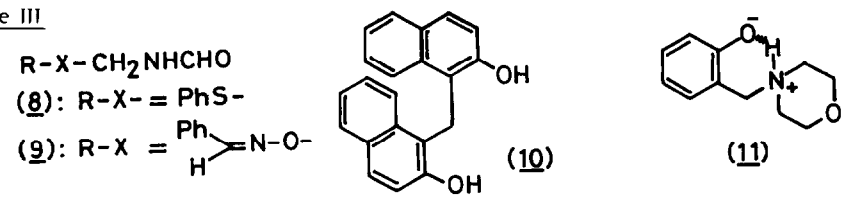
Scheme II



d.n-BuLi,-78°C,RCN,THF e.W-6,Raney-Ni,EtOH,rt,5h

The transfer from (2) to PhSH results in a 72% yield, of (8)[12] which represents a substantial improvement.[11] In the case of oxygen acceptors such as benzaldoxime, 2-naphthol and phenol, the transfer experiments resulted in the isolation of compounds (9) (76%), (10) (74%) and (11) (10%).[12] Whilst the formation of (9) represents the expected transfer, the formation of (10) and (11) can be understood on the basis of acceptance of intermediates arising from fragmentation of (2).

Scheme III



REFERENCES AND FOOTNOTES

1. A.M. van Leusen and J. Schut, Tetrahedron Lett., 285 (1976).

2. In the early part of our work when we used $PhSCH_2NC$ and $pCH_3C_6H_4SCH_2NC$, the entire laboratory was covered with extremely unpleasant odour which took some efforts to dissipate. Some colleagues even complained of illness.

3. For a similar strategy see D. van Leusen, P.H.F.M. Rouwette and A.M. van Leusen, J.Org.Chem., 46, 5159 (1981).

4. Satisfactory analytical results have been obtained for all compounds.

5. (2) : Add formalin (400 mmol) to stirred morpholine (400 mmol) + $HCONH_2$(400 mmol) (20°C; 0.5 h). After 12 h, rt, concentrate (in vacuo), saturate with NaCl, extract with $CHCl_3$(3x100 ml), dry, evaporate to yield N-formamidomethylmorpholine (12,90%),[11] which is used as such for alkylation. Add $PhCH_2I$(220 mmol) to ice cold (12) (152 mmol) in dry $CHCl_3$(100 ml); refrigerate 2 d; white crystals of (2) (71%), mp 156°C.

6. An alternate procedure for (1) and (3), which became available to us after completion of the present work, starts with the commercially obtainable $TosCH_2NHCHO$:2-Naphthyl SH + $TosCH_2NHCHO$—(DMF/NaH)→ (3) (88%, mp 62.5-63.5°C)—($POCl_3/Et_3N$)→ (1) (75%, mp 76-78°C) (A.M. van Leusen, J. Wildeman, J.M. Moskal and A.W. van Hemert, Recl. Trav. Chim. Pays-Bas, 104, 177 (1985); Chem. Abstr., 104, 148443h (1986).

7. (1) : Reflux, 6 h under N_2, (2) (20 mmol) + 2-thionaphthol (20 mmol) + Et_3N(20 mmol) in dry PhH (50 ml). Wash with cold 2N HCl(3x15, 45 ml), H_2O(50 ml), dry, evaporate, chromatograph on silica gel and elute (PhH:EtOAC::1:1) to give (3) (90%) mp 63°C [ir: ν_{max}(KBr) cm^{-1} 3310,1680,1530; nmr: δ($CDCl_3$) 4.5(d,J=7Hz) + 4.7(d,J=7Hz) 2H, in the ratio 7.5:92.5 possibly arising from HN-CHO π barrier); 6.23(br, 1H), 7.3-8.1(m, 8H); ms:m/z 217(M^+)]. Under N_2, reflux 8 h, solution of (3) (20 mmol) + Ph_3P(24 mmol) + dry CCl_4(2 ml) + Et_3N(3.5 ml) in dry $CHCl_3$(50 ml), evaporate, chromatograph over silica gel and elute (PhH) to give (1) (80%); mp 75°C; ir: ν_{max}(KBr) cm^{-1} 2140; nmr: δ($CDCl_3$) 4.6(2H), 7.4-8.1(m,7H); ms:m/z 199(M^+).

8. (4) : mp 190°C; nmr: δ($CDCl_3$ + DMSO-d_6) 2.25(s,3H), 7.05-7.95(m,9H); ms:m/z 240(M^+). (5) : mp 223°C;ms:m/z 303(M^+ + 1).

9. Stir, rt, 5 h, a solution of 1 mmol of (4) or (5) in dry EtOH (20 ml), with freshly made Raney-nickel W-6(1g) filter, evaporate, chromatograph and elute (EtOAC:MeOH::95:5) to give, (6), (73%), mp 45°C, or by preparative tlc (developer EtOAc) to yield (7) (56%), mp 126°C. The mp and nmr of (6) and (7) were identical to that reported (The Aldrich Library of NMR Spectra, 2, 485D, 487D).

10. Adducts (4) and (5), because of the presence of bulky S-aryl moiety, would undergo regiospecific N-alkylation, thus providing an attractive route to scarce N-protected 5-substituted imidazoles.

11. H. Bohme and G. Fuchs, Chem.Ber., 103, 2775 (1970).

12. (8) : liquid (mp 32°C); ir: ν_{max}(neat) cm^{-1} 3320,1690,1540; nmr: δ($CDCl_3$) 4.6(d,J=7Hz,2H), 7.3(m,6H), 7.9(br,1H). (9):mp 60°C; ir: ν_{max}(KBr) cm^{-1} 3290,1660,1520; nmr: δ($CDCl_3$) 5.22(t,2H), 6.7(br,1H), 7.3-7.7(m,5H), 8.1(d,1H), 8.25(s,1H); ms:m/z 178(M^+). (10) mp 196°C (lit.202°C, W.J. Burke, M. Kolbezen and W. Stephens, J.Am.Chem.Soc., 74, 3601(1952). ms:m/z 300(M^+). (11): mp 90°C; nmr: δ ($CDCl_3$) 2.5(m,4H), 3.7(m,6H), 6.6-7.4(m,4H), 8.3(br,1H); ms:m/z 193(M^+).

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