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SIDE-CHAIN SILYLATION OF HETEROCYCLIC DERIVATIVES. THE SYNTHESIS OF 3-METHYL-5-(TRIMETHYLSILYLMETHYL)-1,2,4-OXADIAZOLE AND THE ATTEMPTED SYNTHESIS OF 3-METHYL-4-NITRO-5-(TRIMETHYLSILYLMETHYL)ISOXAZOLE VIA ORGANOLITHIUM REAGENTS

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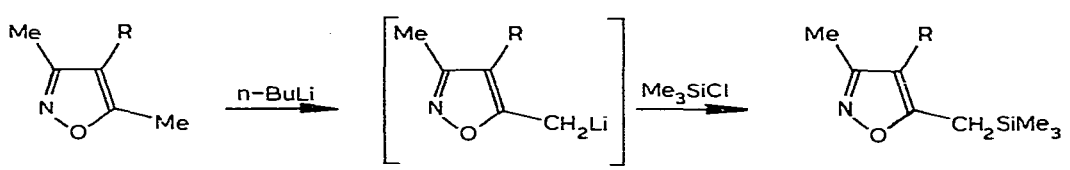
Summary

Silylation of activated heterocyclic systems via treatment with organolithium reagents followed by coupling with Me_3SiCl, leads to the expected product in the case of 3,5-dimethyl-1,2,4-oxadiazole, whereas for 3,5-dimethyl-4-nitroisoxazole the predominant reaction is addition of the lithiating agent, to give after work-up 3,5-dimethyl-5-butyl-4-nitro-4,5-isoxazoline.

Introduction

It has been previously shown that both 3,5-dimethyl-(I) and trimethyl-isoxazole (II) undergo selective side-chain metallation at the C(5) methyl group upon treatment with n-BuLi [1,2]; coupling of the resulting lithiomethyl derivatives (III and IV) with Me_3SiCl gives the corresponding (trimethylsilylmethyl)isoxazoles (V and VI) in good yields [2].

SCHEME 1.



(I) R = H
(II) R = Me

(III) R = H
(IV) R = Me

(V) R = H
(VI) R = Me

We describe below some attempts to extend this method to similar compounds

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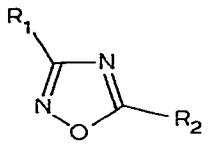
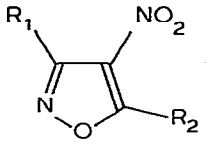
in which the methyl groups in the 5 position are more acidic, such as 3,5-dimethyl-1,2,4-oxadiazole (VII) and 3,5-dimethyl-4-nitroisoxazole (X). The acidity of the methyl groups in these systems is confirmed for the first of these compounds by its reactivity in hydrogen exchange [3], and for the latter by the ease of its base-catalysed condensation with aromatic and heteroaromatic aldehydes [4].





(VII) $R_1 = R_2 = Me$

(VIII) $R_1 = Me$; $R_2 = CH_2SiMe_3$

(IX) $R_1 = R_2 = CH_2SiMe_3$

(X) $R_1 = R_2 = Me$

(XI) $R_1 = Me$; $R_2 = CH_2SiMe_3$

Our interest in compounds VIII and XI was stimulated by the synthetic importance of reactive silylated heterocycles as heterocyclic equivalents of carbanions [5], and by the possibility of employing them as potential synthons for new organosilicon derivatives.

Results and discussion

Compound VII reacted smoothly with n-BuLi in dry Et_2O to give, after coupling with Me_3SiCl, a good yield of 3-methyl-5-(trimethylsilylmethyl)-1,2,4-oxadiazole (VIII). The replacement of a C(5) methyl proton of VII (^{13}C NMR: 167.6 ppm (C(3)) and 176 ppm (C(5)) with a Me_3Si group as in VIII gives rise to changes in the ^{13}C NMR chemical shifts of the ring carbon similar to those previously observed in the isoxazole series [2].

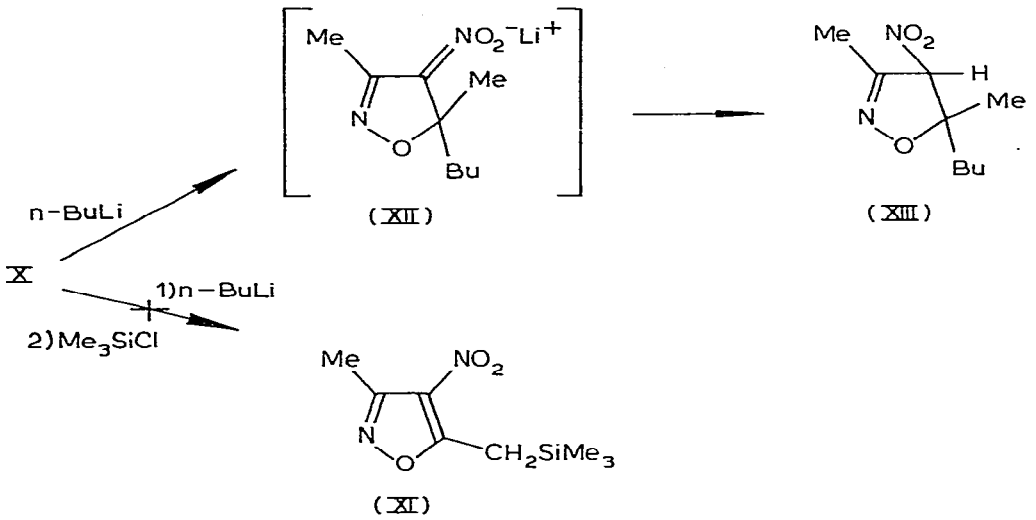
In contrast to the solvent effect reported for the less reactive derivatives I and II [2], replacement of Et_2O by THF lowered the yield drastically and led to formation of several side-products. Amongst these, 3,5-bis(trimethylsilylmethyl)-1,2,4-oxadiazole (IX) was identified by GLC-MS analysis on the basis of its parent ion peak (m/e = 242) and its characteristic fragmentation pattern (m/e = 130, 128, 116, 114) [6]. These results can be rationalized in terms of the different behaviour of n-BuLi in the two solvents, since it approximates to a tetrameric structure in Et_2O but behaves as a dimer in THF [7]. Under the latter conditions the lithiating reagent is a more basic and therefore less selective species, and this gives rise to a more complex product mixture *.

Lithiation of the nitroderivate X was much less straightforward. Irrespective of the metallating reagent (n-BuLi, t-BuLi or LDPA/HMPT), we never obtained the silylisoxazole (XI) after coupling with Me_3SiCl. When compound X was treated with n-BuLi in dry ether (Scheme 2), sizeable amounts of the starting

* In the case of production of the bis-silylated product IX there is a possibility that coordination of Li^+ at the three heteroatoms plays an important role in the metallation of both C(3) and C(5) methyl groups through an "*ortho*" lithiation mechanism [8].

material were recovered, while the isoxazoline (XIII) was isolated as the predominant product, and was characterized by GLC-MS, ^{1}H NMR and elemental analysis.

SCHEME 2.



The side-chain lithiation expected on the basis of the high acidity of the methyl hydrogens is thus much less favoured than nucleophilic attack of the butyl group at position 5 of the isoxazole ring leading to the salt XII. It seems that the 5-methyl group is not metallated during the reaction, and the same conclusion was reached from quenching with D_2O or MeI. Attempts are now being made to generate side-chain carbanions from X by other routes.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (with tetramethylsilane as internal standard) on Perkin-Elmer R 32 and Varian XL 100 spectrometers, respectively. Mass spectra were obtained with a Varian MAT 111 instrument. Ether and THF were dried by distillation from sodium wire and $LiAlH_4$.

3-Methyl-5-(trimethylsilylmethyl)-1,2,4-oxadiazole (VIII)

1.6 *M* n-Buthyllithium in hexane (0.025 mol) was added dropwise under N_2 to a stirred solution of 3,5-dimethyl-1,2,4-oxadiazole (VII) (0.025 mol) in dry ether (60 ml), the temperature being kept below —60°C during the addition. After 30 min at —70°C, chlorotrimethylsilane (0.025 mol) in dry ether was added at such a rate as to keep the temperature below —50°C and the mixture was then allowed to warm to room temperature and set aside overnight. The resulting mixture was carefully evaporated and the residue treated with dry benzene (50 ml). The small amount of solid which separated was filtered off, and the filtrate was evaporated to yield an oil, which was distilled under reduced pressure to give compound VIII (2.50 g, 60%), as a clear colourless oil (b.p. 80—82°C/0.5 mmHg). Found: C, 49.75; N, 16.27; H, 8.30. $C_7H_{14}N_2OSi$

calcd.: C, 49.37; N, 16.45; H, 8.25%. ^{1}H NMR: 0.13 (s, 9 H, $SiMe_3$); 2.28 (s, 3 H, $C(3)H_3$); 2.30 ppm (s, 2 H, CH_2SiR_3); ^{13}C NMR: 2.8 ($Si(CH_3)_3$); 11.3 (3-Me); 17.6 (CH_2SiR_3); 166.7 (C(3)); 178.9 ppm (C(5)).

Reaction of 3,5-dimethyl-4-nitroisoxazole (X) with n-BuLi and Me_3SiCl

1.6 *M* n-butyllithium in hexane (0.025 mol) was added dropwise under N_2 to a cold (—20°C) stirred solution of X (0.025 mol) in dry ether (20 ml). After 1 h at this temperature, Me_3SiCl (0.05 mol) was added, and the mixture was allowed to warm to room temperature. The GLC-MS analysis of the crude reaction mixture did not reveal any trace of side-chain silylated products. After addition of 1 ml of water, the ethereal solution was dried and evaporated; unchanged starting material was then removed by sublimation to give 2.5 g (50% yield) of crude 3,5-dimethyl-5-butyl-4-nitro-4,5-isoxazoline (XIII). High vacuum distillation afforded XIII as a pale yellow oil (b.p. 70—73°C/0.1 mmHg) that decomposed on standing after several days; mass spectrum (M^+) *m/e* 200 ^{1}H NMR: 0.88 (m, 3 H); 1.30 (m, 9 H); 2.00 (s, 3 H, 3-Me); 5.35 ppm (m, 1 H, 4-H); Found: C, 52.80; H, 8.25; N, 13.97. $C_9H_{16}O_3N_2$ Calcd.: C, 54.00; H, 8.00; N, 14.00%.

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