The Direct Generation of *N*-Acyl Formimidate Methylides. An Efficient Approach to the Synthesis of Pyrrolidine Derivatives

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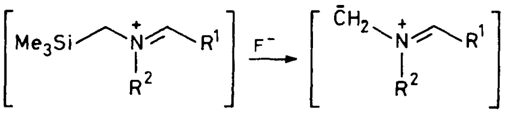
The reaction of silyl-formamidines and silyl-thioformimidates with acyl fluorides gives *N*-acyl imidate methylides which have been successfully trapped with several dipolarophiles to afford pyrrolidine derivatives in high yields.

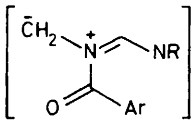
Recently interest has been shown in synthetic methods for generating imidate methylides by desilylation of appropriately substituted immonium cations [*e.g.* (1) → (2)].[1,2] In this communication we now report on the direct generation and subsequent interception of 1,3-dipolar nitrogen ylides corresponding to the general structures (3) and (4).

Treatment of trimethylsilylmethyl isocyanide (5)† with a variety of amines or thiols in the presence of a copper catalyst afforded the corresponding formamidines or thioformimidates [*e.g.* (6) or (7)] in 92 and 94% yields, respectively.[3] *N*-Acylamidate and *N*-acylimidate methylides [*e.g.* (8a) and (8b), respectively] are accessible in a straightforward manner *via* the exposure of formamidines or thioformimidates of this general type to acyl fluorides in acetonitrile solution.‡ Hence, treatment of the formamidine (6) or the thioformimidate (7) with the requisite acyl fluoride in the presence of dimethyl fumarate (1.15 equiv.) in acetonitrile furnished the *N*-acylpyrrolidines (9a) (73%) or (9b) (76%), respectively.§ In contrast to these observations, treatment of either (6) or (7) with acyl chlorides under analogous conditions led to incomplete desilylation and the formation of numerous products. Moreover, exposure of the silylimine (10a) to *p*-nitrobenzoyl fluoride in the presence of dimethyl acetylenedicarboxylate under a variety of experimental conditions led to the formation of intractable mixtures of products. These results contrast sharply with the reported behaviour of the silylimine (10b) in the presence of acyl chlorides[4] suggesting that the latter constitutes a special case.

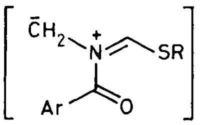
The well established propensity of organic isocyanides to combine with acyl chlorides leading to the formation of α-oxo-imidoyl chlorides[5] suggested that an analogous reaction should be possible between the isocyanide (5) and an acyl fluoride. In principle, this reaction might serve as a method for the generation of nitrile ylides *via* elimination of trimethylsilyl fluoride. In agreement with this idea, treatment of the isocyanide (5) with *p*-nitrobenzoyl fluoride and dimethyl acetylenedicarboxylate (1 equiv. of each) in toluene at 80 °C provided the pyrrole (13) (82% yield) *via* the transient dipole (12).¶



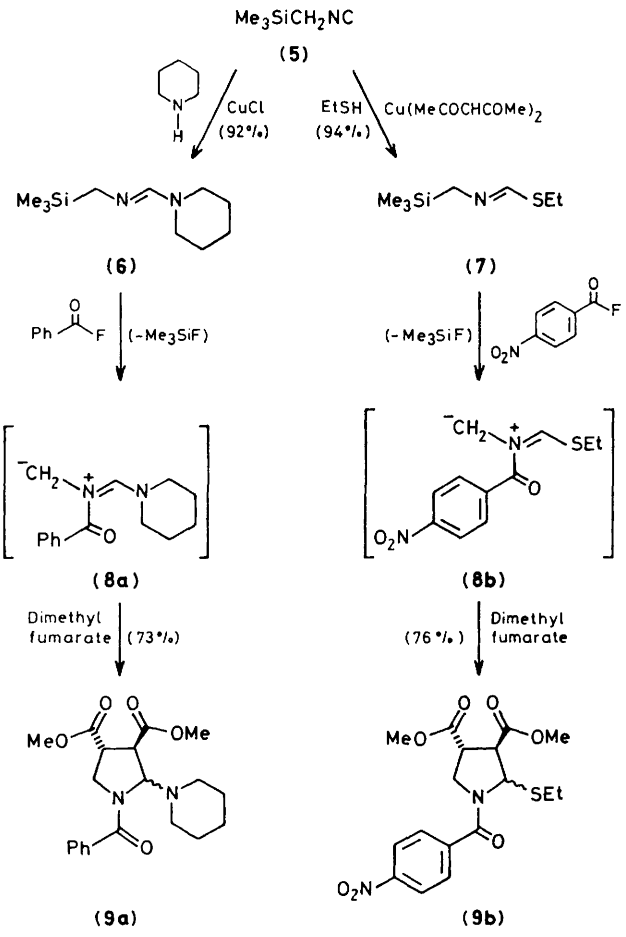
(1) (2)



(3)



(4)



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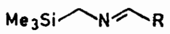
† Trimethylsilylmethyl isocyanide (5) can be conveniently prepared in multigram quantities by lithiating methyl isocyanide [BuLi (1 equiv.), $(MeO)_2CH_2$, −78 °C (45 min)] followed by silylation [Me_3SiCl (2 equiv.), −78 → 25 °C (1 h)]. Careful fractional distillation of the solvent followed by distillation of the residue affords pure (5), b.p. 75—77 °C (70 mmHg), in 45—50% yield.

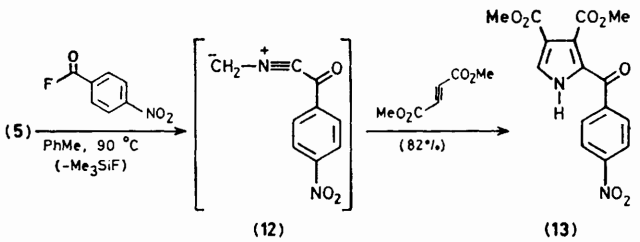
‡ A typical experimental procedure is as follows. A solution of (6) (1.00 mmol) in acetonitrile (1.5 ml) was added dropwise *via* mechanical syringe to a stirred solution of *p*-nitrobenzoyl fluoride (1.00 mmol) and dimethyl fumarate (1.15 mmol) in acetonitrile (2.5 ml) maintained at 45 °C over the course of 3 h. Stirring was continued at 45 °C for an additional 2 h. The solvent was then evaporated off and the residue subjected to preparative t.l.c. on silica gel (CH_2Cl_2–C_6H_{14}–EtOAc 2:2:1) to provide (9b), 299 mg (76%).

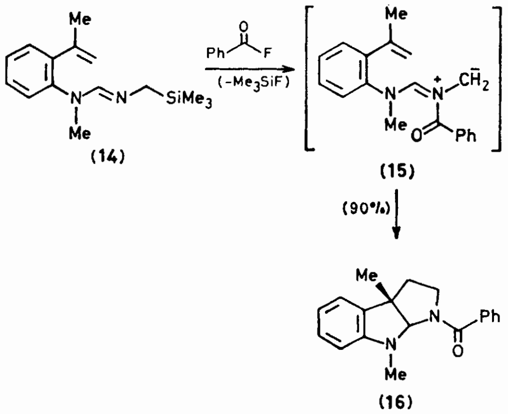
§ Satisfactory spectral and elemental analyses were obtained for all the new compounds reported. All reported yields refer to distilled or chromatographed products. The *N*-acyl pyrrolidines, (9a) and (9b), were obtained as a mixture of epimers.

¶ The attempted use of acyl fluorides which are less reactive than *p*-nitrobenzoyl fluoride has not proved to be promising so far.



(10a); R = CH_2CH_2Ph
(10b); R = Ph





The failure of phenylacetylene and pent-1-yne to serve as dipolarophiles in the intermolecular trapping of the imidate methylides, (**8a**) and (**8b**),** does not preclude the possibility that nonactivated dipolarophiles might take part in intramolecular cyclizations. In confirmation of this hypothesis, addition of the formamidine (**14**) over 4 h to a solution of benzoyl fluoride in acetonitrile maintained at 45 °C afforded the tricyclic aminal (**16**) (m.p. 137—138 °C) *via* the intermediate (**15**) in 90% yield.

We conclude that the direct generation of *N*-acylimidate methylides by way of the methods described in this report constitutes an expedient and versatile alternative to the existing procedures.[1-3]

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** In contrast to the successful interception of the imidate methylides, (**8a**) and (**8b**), by electronically deficient dipolarophiles, efforts to trap these species with unactivated dipolarophiles (*e.g.* phenylacetylene or pent-1-yne) have so far been unsuccessful.