

Chemistry of Aminoketene Dithioacetals: Preparation of Protected α -Amino Aldehydes and Ketones and Formation of Nitrogen Heterocycles

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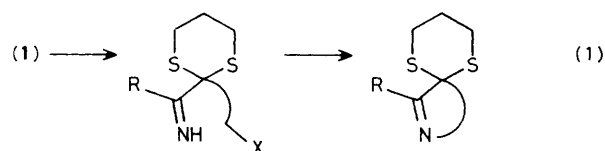
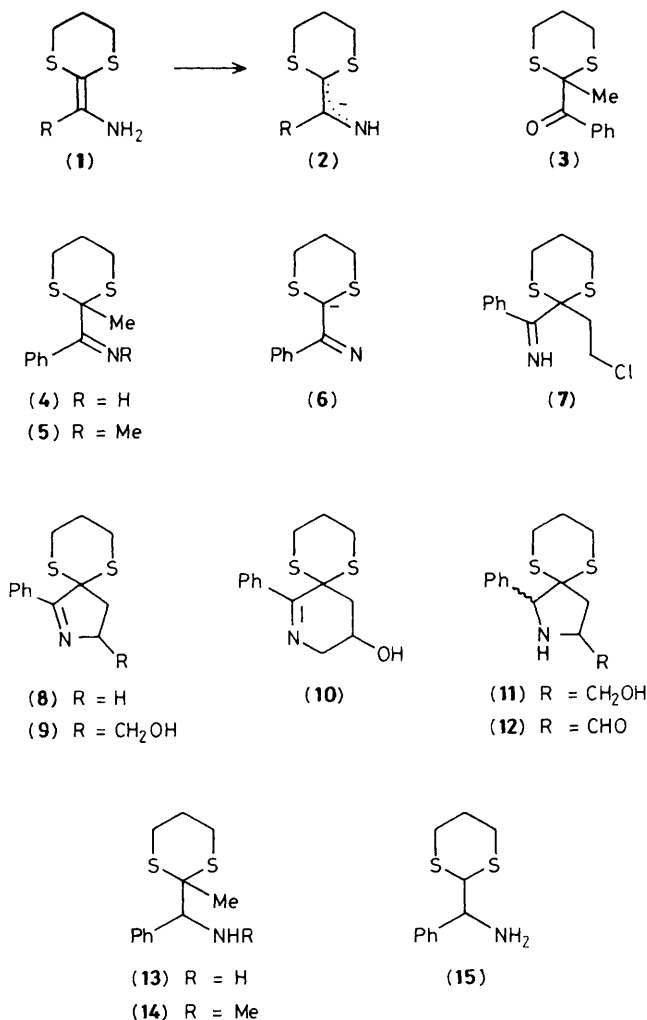
The ambident anion (**2**) derived from primary aminoketene dithioacetal (**1**, R = Ph) reacts with alkyl halides at the carbon atom to give remarkably stable primary imines which may be reduced to give protected α -amino ketones using borane in quantitative yield, and under similar conditions aminoketene dithioacetal (**1**, R = Ph) gives the protected α -amino aldehyde (**15**); anion (**2**) reacts with the bis-electrophile epichlorohydrin to give the nitrogen heterocycle (**9**) in 80% yield, and other related chemistry is also reported.

Recently we reported the preparation of primary aminoketene dithioacetals (**1**)¹ and their reactions with α,β -unsaturated ketones.² These compounds, which are at once primary enamines and ketene thioacetals, exhibit a pronounced ambident nucleophilicity. Thus, while acylation of (**1**) occurs exclusively at the nitrogen atom, treatment of (**1**, R = Ph) with *n*-butyl-lithium at -40°C in tetrahydrofuran (THF) solution followed by addition of methyl iodide and hydrolytic work-up (0.1 M HCl) gives the mono-protected diketone (**3**).

We have discovered that use of a saturated aqueous solution of ammonium chloride in place of dilute acid in the work-up procedure allows isolation of the primary imine (**4**) in quantitative yield. This compound exhibits remarkable stabil-

ity even at room temperature, perhaps owing to steric hindrance to nucleophilic attack,³ and may be purified by column chromatography on silica gel without any unusual precautions. Treatment of imine (**4**) with *n*-butyl-lithium (1 equiv.) followed by methyl iodide gives secondary imine (**5**) in good yield (63%). The primary aminoketene dithioacetal (**1**, R = Ph) is therefore an equivalent of dianion (**6**). We sought to utilise this property in a synthesis of nitrogen heterocycles by sequential reaction of (**1**) with one equivalent of base, a bis-electrophile, and a second equivalent of base to effect cyclisation, reaction (1).

Treatment of anion (**2**) with a large excess of 1,2-dichloroethane at -40°C gave not the primary imine (**7**) but the



heterocycle (8). This we rationalise by postulating a proton exchange between the imine (7) and anion (2). Further, addition of one equivalent of epichlorohydrin to two equivalents of (2) at -78°C gave a mixture of heterocyclic products (9) and (10) in 94% yield and in a ratio of *ca.* 5:1, one equivalent of (1, R = Ph) being recovered. The ratio of products decreased to 2:1 as the temperature was increased to -25°C . The structures of (9) and (10) were distinguished by reduction of the imine group of (9) using borane-THF complex to give (11) (90%) followed by alcohol oxidation using the Swern procedure⁴ to give the aldehydes (12) as a mixture of isomers (32%).

Reduction of imines (4) and (5) does not occur using hydride reagents, but proceeds quantitatively with an excess of diborane at room temperature yielding the protected α -amino ketones (13) and (14). Similar treatment of (1, R = Ph) at 50°C followed by 5 M HCl at reflux gave the protected α -amino aldehyde (15) in 71% yield. Compound (15) is conveniently isolated as the hydrochloride salt and may be stored indefinitely.

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References

- 1 P. C. B. Page, M. B. van Niel, and P. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1985, 742.
- 2 P. C. B. Page and M. B. van Niel, *J. Chem. Soc., Chem. Commun.*, 1987, 43.
- 3 A. Dondoni and G. Barbaro, *J. Chem. Soc., Chem. Commun.*, 1975, 761.
- 4 A. J. Mancuso, S. L. Huang, and D. Swern, *J. Org. Chem.*, 1978, 43, 2480.