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

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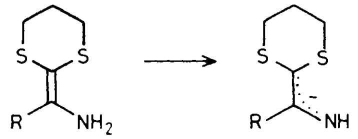
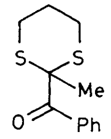
The ambident anion (**2**) derived from primary aminoketene dithioacetal (**1**, R = Ph) reacts with alkyl halides at the carbon atom to give remarkably stable primary imines which may be reduced to give protected α-amino ketones using borane in quantitative yield, and under similar conditions aminoketene 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.

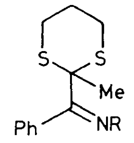
Recently we reported the preparation of primary aminoketene dithioacetals (**1**)[1] and their reactions with α,β-unsaturated ketones.[2] These compounds, which are at once primary enamines and ketene thioacetals, exhibit a pronounced ambident nucleophilicity. Thus, while acylation of (**1**) occurs 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**).

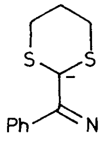
We have discovered that use of a saturated aqueous solution of ammonium chloride in place of dilute acid in the work-up procedure allows isolation of the primary imine (**4**) in quantitative yield. This compound exhibits remarkable stability even at room temperature, perhaps owing to steric hindrance 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).

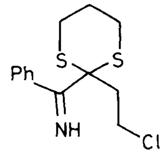
Treatment of anion (**2**) with a large excess of 1,2-dichloroethane at −40 °C gave not the primary imine (**7**) but the

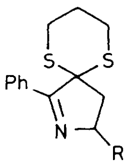

(1) **(2)**

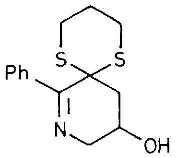

(3)

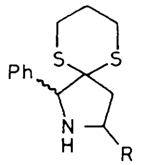

(**4**) R = H
(**5**) R = Me

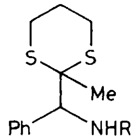

(**6**)

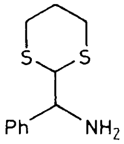

(**7**)

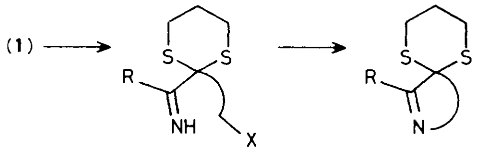

(**8**) R = H
(**9**) R = CH_2OH


(**10**)


(**11**) R = CH_2OH
(**12**) R = CHO


(**13**) R = H
(**14**) R = Me


(**15**)


(1)

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 procedure[4] 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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