Vicarious nucleophilic substitution of hydrogen in electrophilic aldimines: synthesis of enamines substituted with electron-withdrawing groups

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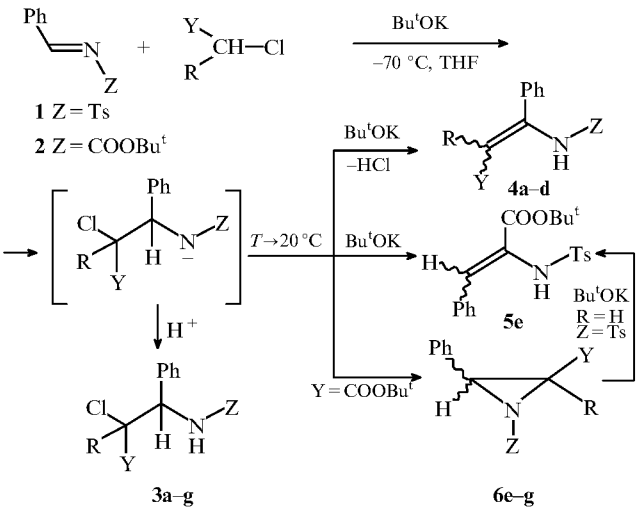
Strongly electrophilic benzaldimines react with α-chlorocarbanions giving two types of substituted enamines, *via* vicarious nucleophilic substitution of hydrogen or a cyclisation-ring opening process.

Carbanions containing leaving groups X at the carbanionic centre react with nitroarenes *via* formation of σ^H adducts followed by base-induced β-elimination of HX to give products of the vicarious nucleophilic substitution (VNS) of hydrogen.[1] A similar reaction can occur between these carbanions and electrophilic alkenes;[2] however, such a process is less common because the initial adducts are often protonated to give products of the Michael addition or intramolecular nucleophilic substitution takes place furnishing cyclopropane derivatives — reactions which usually do not occur in the σ^H adducts to nitroarenes.

An analogous reaction could, in principle, occur at electrophilic carbon–heteroatom double bonds, provided there is a hydrogen at the carbon atom. In analogy to the requirements formulated for VNS reactions in electrophilic alkenes[2] one would expect that this process would be feasible in aldimines R–CH=N–Z when Z assures efficient delocalization of the negative charge and R favours abstraction of the proton necessary for the base-induced β-elimination. One example of such a process between *N*-phenylbenzaldimine and chloromethanesulfomorpholide carbanion has already been reported.[3] A similar reaction of carbonyl-stabilized sulfonium ylids with *N*-arylimines has also been published.[4] However, in both these cases Z — an aryl group — possessed rather poor negative charge stabilisation ability and the mechanistic features were not fully recognized.[3]

The requirements promoting the VNS-type reaction are met by Ph–CH=N–Z where Z = SO_2Ar **1** and Z = $COOBu^t$ **2**; these compounds are readily available *via* condensation of benzaldehyde with *p*-toluenesulfonamide or *tert*-butyl carbamate, respectively.[5] The reaction of these imines with carbanions derived from α-chlorosulfone, esters of α-chlorocarboxylic acids and chloroform, generated in the presence of Bu^tOK at low temperature, resulted in the formation of the anions of adducts **3a–g** which were stable at –70 °C no matter whether an excess of the base was used or not; they could be isolated and characterized (Scheme 1, Table 1) after protonation.[†,‡] When the reaction was carried out in the presence of a large excess of Bu^tOK and the temperature was allowed to rise to 20 °C the adducts **3a–e** underwent a transformation leading to the enamines **4** or **5**, depending on the nature of the carbanion-stabilizing groups. The adducts of the chlorosulfone and chloroform formed enamines **4a–d**, apparently *via* the base-induced β-elimination of HCl. Thus, in this case the vicarious substitution of hydrogen occurs according to the general Scheme 1 of this reaction.[1]



Scheme 1

On the other hand, the enamine **5e** produced from the adduct of the chloroacetate carbanion was formed *via* a different pathway: a process involving a cyclization–ring opening sequence. The difference in the reaction pathways observed can be easily rationalized the differing susceptibility of the chlorine atoms in adducts **3a–d** and **3e** to nucleophilic substitution, hence the cyclization reaction.

Experimental support for the above explanation arose from observations that the anions of adducts **3e–g** (Y = $COOBu^t$), obtained at low temperature, when warmed to 20 °C without any excess of base underwent cyclisation leading to the aziridine derivatives **6**, whereas in the case of **3a–d** the adducts were recovered after the same procedure. Furthermore, the aziridine **6e** treated with Bu^tOK at room temperature gave corresponding enamine **5e** in good yield, which is in accord with earlier reports on the base-promoted aziridine ring-opening reactions,[6,7] whereas **6g** in which there is no acidic proton at C-2 necessary for the ring-opening process (R = Me) remained unchanged. This result proves that the alternative route to formation of enamines **4** by abstraction of the C-3

Table 1 Reactions of imines **1** and **2** with α-chlorocarbanions.

Z	Y	R	Product, yield (%)[a]		
			adduct	enamine	aziridine
Ts	Cl	Cl	**3a**, 61	**4a**, 40	[b]
Ts	Ts	H	**3b**, 68	**4b**, 68	[b]
$COOBu^t$	Cl	Cl	**3c**, 81	**4c**, 53	[b]
$COOBu^t$	Ts	H	**3d**, 93	**4d**, 70	[b]
Ts	$COOBu^t$	H	**3e**, 65	**5e**, 21[c] 60[d]	**6e**, 73
$COOBu^t$	$COOBu^t$	H	**3f**, 78	[b]	**6f**, 79
$COOBu^t$	$COOBu^t$	Me	**3g**, 68	[b]	**6g**, 53

[a] Isolated yields, mixture of two stereoisomers. [b] Not formed. [c] Obtained directly from **1**. [d] From **6e**.

† General procedure for the reactions of **1** and **2** with α-chloro CH-acids. To a stirred solution of Bu^tOK (1.1 or 2.5 mmol) in dry THF (7 ml) was added a solution of the CH-acid (1 mmol) and aldimine **1** or **2** (1 mmol) in THF (1 ml), dropwise at –70 °C. The mixture was stirred for 30 min at this temperature to obtain the *adducts*, or after 5 min the cooling bath was removed, the reaction mixture was allowed to warm up to room temperature and stirred for 1 h to obtain the *enamines* (excess of Bu^tOK) or the *aziridines* (with equimolar amount of the base). After the reaction was complete the mixture was poured into cold aqueous NH_4Cl, slightly acidified with dilute HCl and worked-up by standard methods including column chromatography on SiO_2.

‡ All new compounds gave the expected ^1H NMR and IR spectra and satisfactory elemental analyses. The structures of enamines **4b,d** and **5e** were unambiguously proved by chemical transformations: acidic hydrolysis to acetophenone derivatives (for **4**) and catalytic hydrogenation to phenylalanine derivative[6,8] (for **5**).

proton and subsequent ring opening, does not occur under these reaction conditions. Unexpectedly, the aziridine **6f**, although possessing an acidic proton, was found to be stable toward an excess of Bu^tOK even at room temperature; thus it was the final reaction product.

The results obtained show a certain similarity between the reactions of electrophilic imines to those of highly electrophilic alkenes.[2] The influence of the structure of the imine, carbanion, leaving group and the reaction conditions on the possible reaction pathways, *i.e.* VNS and aziridine ring opening, is now under investigation.

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