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Tandem radical and non-radical reactions mediated with thiols—a new method of cleavage of allylic amines

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Received (in Cambridge, UK) 26th October 2001, Accepted 3rd December 2001
First published as an Advance Article on the web 8th January 2002

Thiyl radical promotes the isomerisation of allylic amines into enamines *via* two consecutive hydrogen atom abstraction steps, and the subsequent polar addition of the corresponding thiol to the enamine results in the cleavage of the C–N bond *via* a thioaminal intermediate: this reaction provides a mild, metal-free methodology for the deprotection of allylated primary and secondary amines.

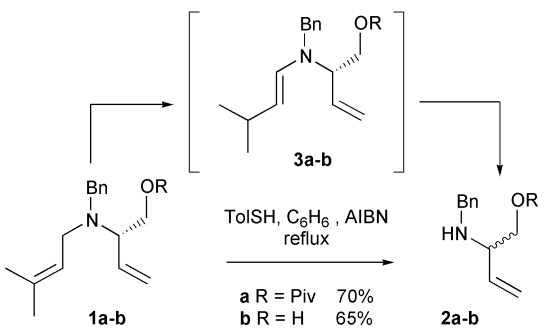
Our interest in sulfur-centered radical mediated cyclisations of 1,6-dienes[1] led us to investigate the addition of thiocresol to dienes **1a** and **1b**. These reactions reported in Scheme 1 led to an unexpected result: the only products, isolated in 70 and 65% respectively, were amines **2a** and **2b** resulting from the cleavage of the primary allylic C–N bond. No trace of any cyclisation product was detected. It is noteworthy that the amine that would result from the cleavage of the secondary allylic C–N bond was not formed either. Control experiments have been carried out. When **1a** was heated alone, or with thiocresol, but in the absence of AIBN, nothing happened. When AIBN was added to the mixture, the deprenylation occurred. Heating the substrate with AIBN in the absence of thiol did not give rise to any transformation either. These results point strongly to a radical chain mechanism involving thiyl radicals. The reaction is likely to proceed, *via* the migration of the double bond, through enamines **3** that would be hydrolysed upon treatment.

Although the very first experiments were conducted with a syringe pump monitored addition of thiol and AIBN to the substrate, the same results could be obtained mixing all the reagents together at once. In order to get a more accurate picture of both the mechanism and the scope and limits of the reaction, other substrates were submitted to the following experimental conditions: refluxing a 0.06 M solution of the allylic amine, with 1.2 equivalent of thiocresol and AIBN (20 mol % in two portions), over 4 h. Starting from either **4** or **8** led cleanly to the formation of thioaminal **7** or **9** respectively, identified in each case as the single product from the ^{1}H NMR spectrum of the crude mixture [Ha signal appears as a dd at 4.34 ppm (J = 8.9 and 5.9 Hz) in **7**, and as a pseudo t at 4.26 ppm (J = 7.5 Hz) in **9**]; the chemical shift of the corresponding carbon is 76.6 ppm in **7** and 82.0 ppm in **9**) (Scheme 2).

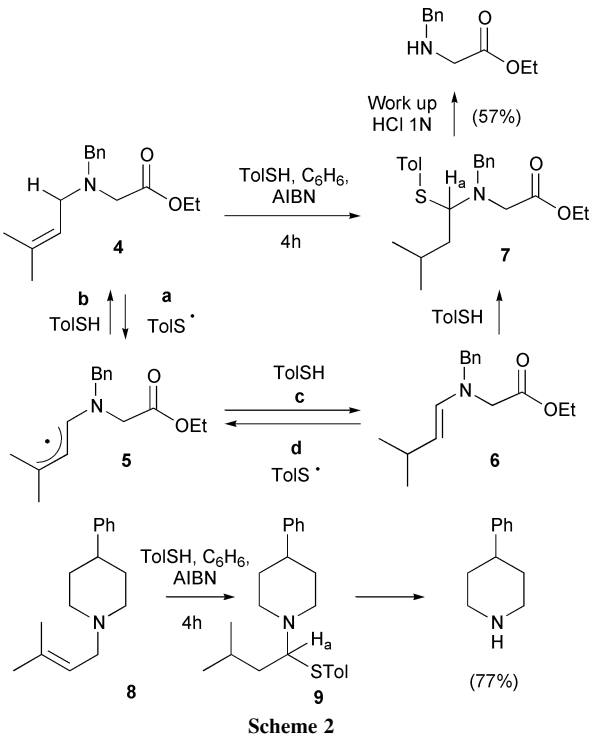
The migration of the double bond can be explained on the grounds of the mechanism proposed in Scheme 2. The thiyl radical abstracts the allylic hydrogen atom which leads to **5**. According to thermodynamical data, this reaction should be nearly thermoneutral, or slightly endothermic [BDE (TolS–H) = 80–83 kcal mol^{-1};[2] BDE (C–H) = 82.6 kcal mol^{-1} [3]]. The delocalised radical transfers back a hydrogen atom from thiocresol to give the enamine **6**.[4] Both reactions **a** and **c** are formally reversible. We believe that the equilibrium is displaced owing to the ready addition of the thiol to the enamine.[5]

It is to be noted that the hydrogen atom transfer between the electron rich C–H bond in **4** and the electrophilic thiyl radical is favoured on the grounds of polar effects. The same assumption applies to step **c** where the hydrogen atom is transferred from the thiol—acting here as a ≪ protic ≫ hydrogen atom donor, according to Roberts[6]—to the nucleophilic carbon centered radical.

We have tried to get an experimental probe for the formation of the enamine, from the NMR spectrum of the crude mixture, starting from an aniline derivative which should lead to a less reactive enamine. When the reaction was performed on *N*-methyl *N*-prenyl aniline, the reaction led to two products, the unchanged substrate and the enamine in a 73 : 27 ratio. In this case, the enamine was not basic enough to react with thiocresol, only a trace amount of the cleavage product was detected. The presence of the enamine in the crude reaction mixture was characterised by the signals corresponding to the vinylic protons β- to the nitrogen atom in the two isomers (5.80 ppm and 5.30 ppm respectively).



Scheme 1



Scheme 2

DOI: 10.1039/b109781d

According to our rationalisation, the more acidic the thiol, the more efficient the addition of the thiol to the enamine and, as a consequence, the faster the cleavage of the C–N allylic bond. The comparison of reactions conducted, for exactly 4 h, on amine **10** (Fig. 1) with thiocresol, thioglycolic acid methyl ester, and octanethiol respectively, is in agreement with this proposal. Only the first reaction involving the most acidic thiol was completed. The conversion to dicyclohexylamine was 100% in the first case, 78% in the second case, and 57% in the third one.

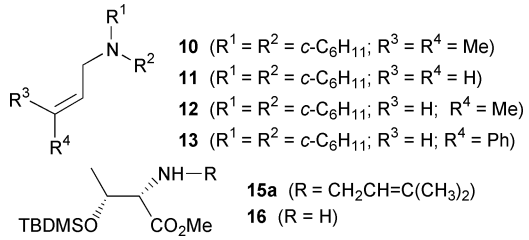


Fig. 1

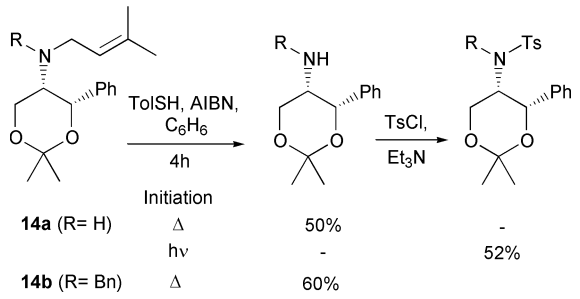
This reaction is general and the cleavage occurred, with moderate to good yields, with different allylic groups like crotyl, allyl or cinnamyl (Table 1). The phototochemical initiation worked also, but gave a lower yield in our hands.

Table 1 Cleavage of amines **12**–**15** with TolSH[a]

	Isolated yield %	
Substrate	Δ	*hν*
10	97	64
11	63	
12	95	
13	70	

[a] Conditions: 0.06 M solution of substrate in PhH; ToISH (1.2 equiv.); AIBN (20 mol% in 2 portions); reflux

Secondary allylic amines behaved similarly, as shown in Scheme 3. Starting from **14a**, the yield was identical (50%), whatever the initiation (thermal or photochemical), and whatever the work up (acidific work up, or trapping of the primary amine by tosyl chloride).[7] When the benzylated amine **14b** was submitted to the same experimental conditions, the reaction led to a single diastereoisomer in 60% yield. In this case, the yield was slightly higher and the reaction mixture was very clean, no other product could be detected. This might be explained by the fact that the stability of the α-aminoalkyl radical increases with the substitution at the nitrogen atom,[8] this should accelerate the abstraction of the allylic hydrogen atom compared to the competitive abstraction of the benzylic hydrogen atom. In the case of **15a**, as with **14a**, the yield in **16** was moderate (44%), but again no epimerised product was isolated nor identified. This is a totally surprising result since, under such conditions one would have expected a capto-dative position to be epimerised [BDE (capto-dative C–H) = 82–83 kcal mol^{-1} [9]].



Scheme 3

As regards to the limits, it must be noted that the cleavage does not take place when the nitrogen atom bears an electron withdrawing group like Ts or Boc.

These results are closely related to those reported by Roberts on the isomerisation of allylsilyl ethers to silylenol ethers.[10] Under our experimental conditions allyl- and prenyl alkyl ethers remained unchanged. In conclusion, the abstraction of the allylic hydrogen atom by thiyl radical promotes the cleavage of allylic amines. The reaction is chemoselective, a primary C–N allylic bond can be cleaved selectively in the presence of a secondary one.[11] This reaction, conducted under relatively mild conditions, complements the methodologies already available in the literature which mainly consist in heavy metal catalysed isomerisations.[12]

Notes and references

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7 Amazingly, no epimerisation at the benzylic position was observed. The analysis of the ^{1}H NMR spectrum of the crude mixture and the moderate yield suggest that once formed, the benzylic radical might undergo a fragmentation leading to unidentified products, instead of being reduced.

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11 This might be due to the minimisation of the allylic strain leading to a conformation around the secondary C–N bond unfavourable to the hydrogen abstraction, as in the case of allylic ethers *(cf*. ref. 10).

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