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Catalyzed reactions of α-amino diazoketones with allyl sulfides: a new synthetic protocol for α-amino homoallyl ketones en route to 3-piperidinol alkaloids

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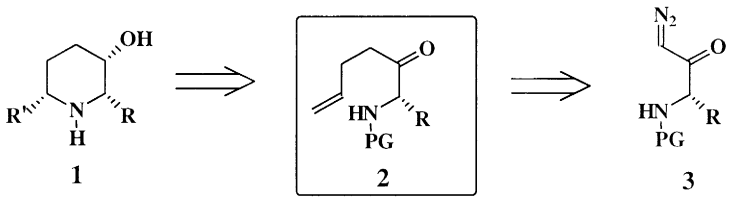
Abstract

$Cu(acac)_2$-catalyzed reactions of enantiopure α-amino diazoketones with allyl sulfides provide a facile synthetic route to α-amino homoallyl ketones via 2,3-sigmatropic rearrangements of the derived allyl sulfonium ylides.

Keywords: α-amino diazoketones; allyl sulfonium ylides; 2,3-sigmatropic rearrangements; α-amino ketones.

The *Cassia* and *Prosopis* species produce a number of 2,6-disubstituted-3-piperidinol alkaloids **1** (e.g. azimic acid, spectaline, julifloridine, prosopinine, etc.)[1] which have attracted much current synthetic attention due to their broad spectrum of biological activities.[2] In a unified synthetic approach towards these alkaloids, we identified the enantiopure α-amino homoallyl ketones **2** as the key retrosynthetic precursors and were in search of an efficient synthetic route towards the latter compounds (Scheme 1).

Enantiopure α-amino homoallyl ketones can be prepared via nucleophilic α-amino acylation reactions of homoallyl lithium with α-amino Weinreb amides[3] or, in the Rapoport-protocol, with NHTos α-amino acids.[4] However, due to the high costs of preparing Weinreb-amides and the need of a large excess of homoallyl lithium in the Rapoport-protocol, these procedures were deemed unsuitable for our present purpose. We, therefore, sought an organometallic-free approach for the preparation of enantiopure α-amino homoallyl ketones and in this letter, we report a conceptually new synthesis of these compounds



Scheme 1.

* Corresponding author.

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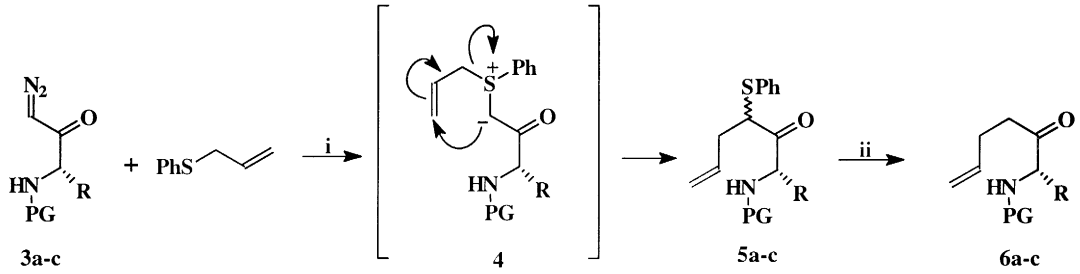
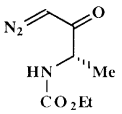
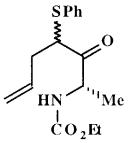
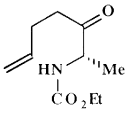
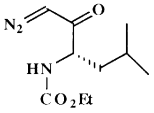
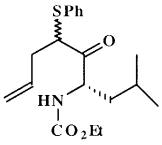
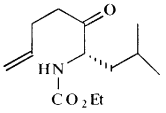
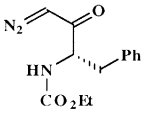
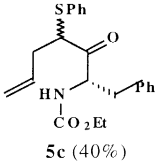
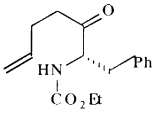
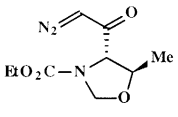
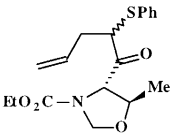
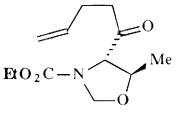
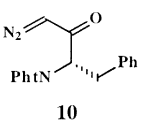
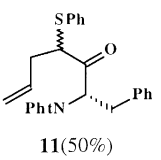


NHPG = $NHCO_2Et$
a: R = Me; **b:** R = *i*-Bu; **c:** R = CH_2Ph

Scheme 2. *Reagents and conditions*: (i) 10% $Cu(acac)_2$, benzene, 80°C, 5 min; (ii) Zn, NH_4Cl, ether, rt, 30 h

Table 1
Synthesis of α-amino homoallyl ketones (Scheme 2)

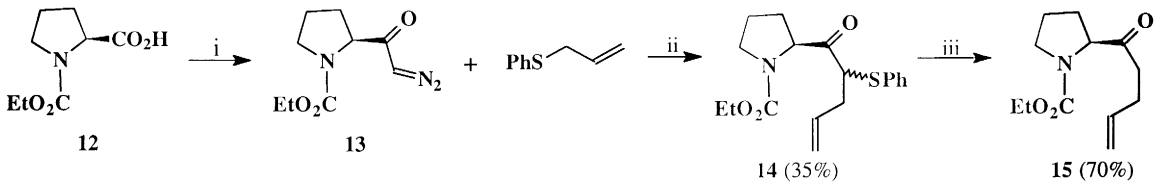
Entry	α-Amino Diazoketones **3,7,10**	α-Amino-α'-thio Homoallyl Ketones **5,8,11**	α-Amino Homoallyl Ketones **6,9**
1	 **3a**	 **5a** (40%)	 **6a** (77%)
2	 **3b**	 **5b** (41%)	 **6b** (98%)
3	 **3c**	 **5c** (40%)	 **6c** (75%)
4	 **7**	 **8** (30%)	 **9** (66%)
5	 **10**	 **11**(50%)	—

via facile 2,3-sigmatropic rearrangements of allyl sulfonium ylides derived from catalyzed reactions of enantiopure α-amino diazoketones **3** with allyl sulfides.

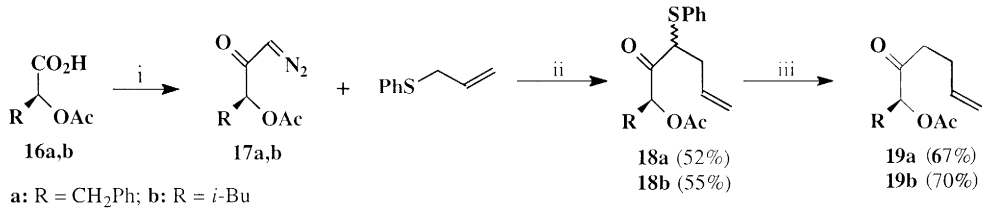
Catalyzed reactions of α-diazoketones with allyl sulfides leading to allyl sulfonium ylides and their 2,3-sigmatropic rearrangements are well documented in the literature.[5] However, apart from a few reactions of diazopenicillanates with allyl chalcogenides,[6] there are no reports on the use of enantiopure α-diazoketones in such sequences. This appeared to be a significant synthetic gap, especially since catalyzed reactions of enantiopure α-diazoketones[7,8] with allyl chalcogenides, via 2,3-sigmatropic rearrangements of the derived ylides, promised a rapid and convergent assembly of functionalized enantiopure building blocks under mild and neutral conditions. Such prospects provided additional impetus for the present investigation.

Catalyzed reactions of allyl phenyl sulfide with enantiopure α-amino diazoketones **3a–c**[7] were examined under a variety of conditions. The best results were obtained with $Cu(acac)_2$ as the catalyst (better than $Rh_2(OAc)_4$) in benzene at 80° *using short contact times* (≤5 min) which, reproducably, led to the rapid formation of the α-amino-α′-thio homoallyl ketones **5a–c** via 2,3-sigmatropic rearrangements of the allyl sulfonium ylides **4** (Scheme 2). Reactions carried out in CH_2Cl_2 or THF (at reflux) gave incomplete conversions, whereas prolonged heating of the reaction mixture or slow addition of **3** to a heated mixture of the allyl sulfide and catalyst did not improve the yields, and in fact, led to increasing amounts of the side products. The yields of these reactions were found to be moderate (Table 1), as is often observed for intermolecular reactions of α-diazoketones with allyl sulfides, and this may be attributed to dimerization problems and/or secondary reactions of the product thioketones with the diazocarbonyl compounds.[9] Nevertheless, the convergent nature of this synthesis, coupled with the ready availability of starting materials, still made it an attractive synthetic sequence. The α-amino-α′-thio homoallyl ketones **5a–c** were all produced as variable mixtures of diastereomers which, without separation, were subjected to desulfurization with Zn/NH_4Cl[10] in ether at rt to produce the desired α-amino homoallyl ketones **6a–c** in good to excellent yields (Scheme 2, Table 1).[11] Raney-Ni could not be used in this desulfurization step since it causes simultaneous saturation of the double bonds in the products. That the enantiomeric purities of the starting α-diazoketones **3** were preserved during this two-step sequence was shown by the following experiment: the α-amino homoallyl ketone **6b**, upon catalytic hydrogenation, produced the corresponding α-amino butyl ketone whose optical rotation value ($[\alpha]_D^{25}$ +35.2, *c* 2, $CHCl_3$) was found to be in good agreement with the α-amino butyl ketone ($[\alpha]_D^{25}$ +33.2, *c* 2.6, $CHCl_3$) independently synthesized via reaction of the *N*-CO_2Et leucinyl Weinreb-amide with *n*-BuLi (THF, −78°C). The $Cu(acac)_2$-catalyzed reaction of the allyl sulfide with the L-threonine-derived oxazolidinyl α-diazoketone **7** (entry 4, Table 1) similarly produced **8** (30%), which was subsequently desulfurized with Zn/NH_4Cl to give the oxazolidinyl homoallyl ketone **9** in 66% yield. *N*-Phthaloyl α-amino diazoketones, e.g. **10**, also reacted with allyl phenyl sulfide in the presence of 10% $Cu(acac)_2$ to produce **11** (50%) (entry 5, Table 1), but desulfurization of the latter proved problematic due to concomitant reduction of its phthaloyl moiety.

The *N*-CO_2Et-L-proline-derived α-diazoketone **13**, via the above two-step sequence, also produced the homoallyl ketone **15** (Scheme 3) which promises to be a useful synthon towards synthesis of various indolizidine alkaloids.



Scheme 3. *Reagents and conditions*: (i) $(COCl)_2$, CH_2Cl_2, then excess CH_2N_2; (ii) 10% $Cu(acac)_2$, benzene, 80°C, 5 min; (iii) Zn, NH_4Cl, ether, rt



Scheme 4. *Reagents and conditions*: (i) Ref. 8; (ii) 10% $Cu(acac)_2$, benzene, 80°C, 5 min; (iii) Zn, NH_4Cl, ether, rt

The enantiopure α-acetoxy diazoketones **17a**,**b**,[8] readily prepared from the α-hydroxy acid chiral pool, also participated in this two-step sequence to produce the α-acetoxy homoallyl ketones **19a**,**b** in somewhat better yields (Scheme 4). The latter promises to have important uses in the synthesis of deoxy-*C*-glycosides.

In summary, we have shown that Cu-catalyzed reactions of enantiopure α-diazoketones with allyl sulfides provide a facile synthetic route to enantiopure α-amino and α-hydroxy homoallyl ketones having broad synthetic ramifications. Allyl selenides also reacted with these diazoketones in a similar fashion,[12] but catalyzed reactions of **3** with benzyl sulfides/selenides have so far produced only complex product mixtures. Syntheses of the 2,6-disubstituted-3-piperidinol alkaloids using the α-amino homoallyl ketones prepared in this work are currently under investigation.

Acknowledgements

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11. All new compounds gave satisfactory spectral data. *A typical procedure*: **(***S***)**-6-Ethoxycarbonylamino-5-oxo-hept-1-ene (**6a**): A solution of **3a** (0.11g, 0.6 mmol), allyl phenyl sulfide (0.18 g, 1.2 mmol) and $Cu(acac)_2$ (10 mol%) in benzene (1.2 ml) was immersed in an oil bath preheated to 80°C. After 5 min, the benzene was removed at reduced pressure and CH_2Cl_2 (5 ml) was added. It was then washed with water, dried and evaporated to give **5a** (diastereomeric mixture) which was purified by preparative TLC over silica gel (30% EtOAc in pet. ether). Activated Zn (0.40 g) and satd NH_4Cl soln (2.5

ml) were added to a solution of **5a** (0.062 g, 0.2 mmol) in THF (3 ml) and the mixture stirred at rt for 30 h, then filtered and the filtrate extracted with CH_2Cl_2 (3×5 ml). Removal of the solvent, followed by preparative TLC over silica gel (15% EtOAc in pet. ether), gave **6a** as a colorless oil (0.031g, 77%); $[\alpha]_D^{28}$ +26.0 (*c* 0.9, $CHCl_3$); IR: 3420, 2980, 1700 (br), 1495 cm^{-1}; ^1H NMR (300 MHz): δ 1.24 (t, 3H, *J*=7 Hz), 1.35 (d, 3H, *J*=7 Hz), 2.35 (q, 2H, *J*=7.2 Hz), 2.50–2.70 (m, 2H), 4.11 (q, 2H, *J*=7 Hz), 4.36 (m, 1H), 4.98–5.07 (m, 2H), 5.42 (br s, 1H), 5.72–5.86 (m, 1H); found: C, 60.51; H, 8.50; N, 7.33. $C_{10}H_{17}NO_3$ requires: C, 60.30; H, 8.54 and N, 7.03%.

12. Sengupta, S.; Das, D., unpublished results.