Tetrahedron Letters 49 (2008) 7355–7357

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Studies in *N*-amino-3-aza Cope rearrangements

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ARTICLE INFO

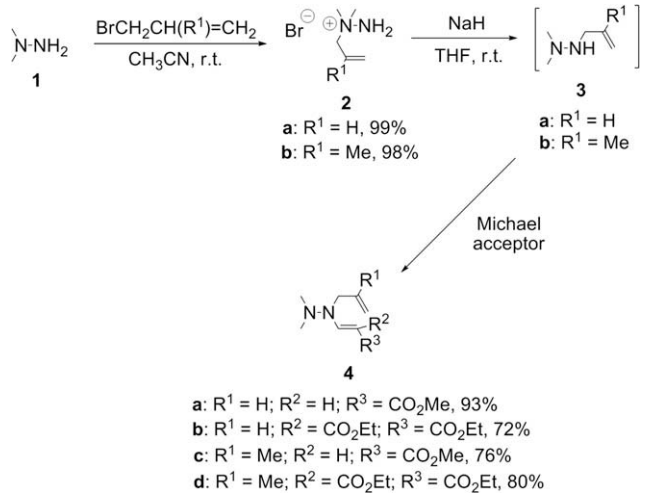
Article history:
Received 16 September 2008
Revised 2 October 2008
Accepted 10 October 2008
Available online 17 October 2008

Keywords:
3-aza Cope
Rearrangement
Thermolysis
Anionic
Hydrazine
Pyrazolone

ABSTRACT

The first examples of a *N*-amino-3-aza Cope rearrangement as well as the first *N*-amino-anion 3-aza Cope rearrangement are reported. These occur in good to excellent yields and in short reaction times.

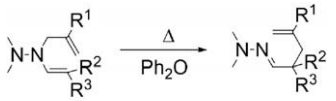
The increasing concern about green processes in organic synthesis makes rearrangements the tool of choice to give access to new functionalities in a molecule with maximum atom economy.[1] One of these rearrangements is the 3-aza Cope rearrangement, which permits an easy way to access imines and aldehydes by hydrolysis of the former. Because these rearrangements normally require drastic conditions[2] (i.e., high temperatures and prolonged reaction times), a large body of work has focused on finding conditions and catalysts for such transformations.[3] For example, the presence of an oxygen attached to the 3-position of these systems enables the rearrangement to be conducted at lower temperatures and in good yields.[4] In this Letter, the first examples of a *N*-amino-3-aza Cope rearrangement as well as its *N*-anion counterpart are reported.



Scheme 1.

The *N*-allyl-*N*-(*N*′,*N*′-dimethyl) enamines (**4a–d**) required for our study were prepared by treating the bromine salts **2a,b** (obtained by reaction of *N*,*N*-dimethylhydrazine (**1**) and the corresponding allyl bromide) with NaH. These underwent a[2,3] (or[1,2]) rearrangement affording the *N*-allyl-*N*′,*N*′-dimethyl-hydrazines (**3a,b**), and were added to the required Michael acceptors without further purification due to their propensity to be oxidized by air[5] (Scheme 1).

Table 1
Rearrangement of *N*-allyl-*N*-(*N*′,*N*′-dimethyl) enamines



4 5

No.	4	Reaction time (min)	Yield of 5 (%)
1	**a**: R^1 = H; R^2 = H; R^3 = CO_2Me	10	73
2	**b**: R^1 = H; R^2 = CO_2Et; R^3 = CO_2Et	5	82
3	**c**: R^1 = Me; R^2 = H; R^3 = CO_2Me	30	79
4	**d**: R^1 = Me; R^2 = CO_2Et; R^3 = CO_2Et	15	80

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doi:10.1016/j.tetlet.2008.10.047

In order to compare the effect of the additional nitrogen in the 3-position with the case when a silyloxy group is present in the same position,[4] enamines **4a–d** were subjected to thermolysis in *o*-dichlorobenzene under reflux at 180 °C, but no reaction was observed after 7 days. It was then decided to raise the temperature to 259 °C by carrying the thermolysis in diphenylether under reflux, and under this condition the rearrangement occurs smoothly with very short reaction times and good yields affording the hydrazones **5a–d** (Table 1).[6]

Despite the fact that the [3,3] sigmatropic rearrangement of the hydrazine derivatives **4a–d** required a higher temperature (259 °C) than the rearrangement of the corresponding hydroxylamine derivatives (180 °C),[4] it was shown that the presence of the additional nitrogen atom in the 3-position still favours the 3-aza Cope rearrangement as evidenced by the short reaction time (Scheme 2a), when compared to a system with an alkyl group connected in the same 3-position (Scheme 2b).[7]

Following the theoretical study of Gilbert and Cousins,[8] which suggests that a negative charge in the nitrogen connected to position 3 of a 3-aza Cope system should favour the rearrangement, it was decided to study the 3-aza Cope rearrangement of pyrazolone derivatives **8a–c**. These should rearrange as described in Scheme 3, and pyrazolone **8a** when treated with base can generate the *N*-amino-anion 3-aza Cope system **8a**′.

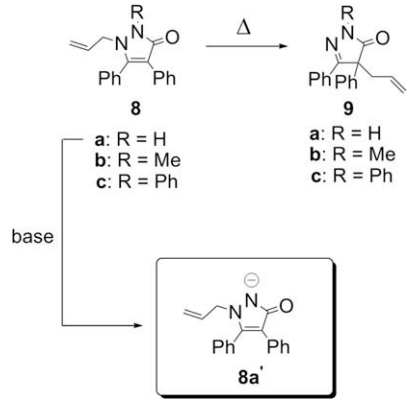
The substrates were prepared by condensation of phenylacetonitrile with ethyl benzoate followed by hydrolysis of the nitrile with HCl in EtOH. Reaction of the ester **11** with the adequate hydrazine afforded the corresponding pyrazolones **12a**–**c**, which were alkylated to give the required allyl pyrazolones **8a–c** (Scheme 4). During the alkylation of pyrazolone **12a** hydrolysis of the BOC group was observed, but no formation of the corresponding alkylation product in this position could be detected.

The pyrazolones **8a–c** were subjected to thermolysis in *o*-dichlorobenzene (180 °C). Pyrazolones **8b** and **8c** afforded the corresponding rearrangement product, while for pyrazolone **8a** no reaction was observed after 7 days. However, when the temperature was raised to 259 °C by refluxing in diphenylether pyrazolone **8a**, the rearranged product **9a** was isolated albeit in only 20% yield after 30 min and accompanied by extensive decomposition (Table 2).

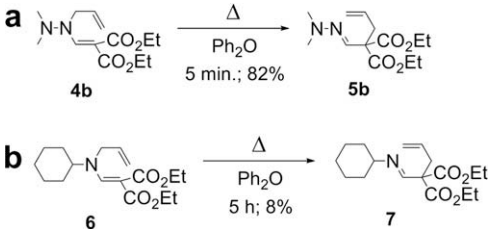
When treated with NaH at room temperature, the pyrazolone **8a** did not show any reactivity. The mixture was then refluxed in *o*-dichlorobenzene (180 °C) affording a product in 60% yield that after characterization was shown not to be the rearrangement product **9a**, but instead the O-alkylated product as a mixture of isomers with a ratio *Z*/*E* of 4.5:1, respectively (Scheme 5).

A possible mechanism for this transformation could involve an initial [3,3] (or [1,3]) rearrangement followed by a retro Claisen rearrangement with subsequent isomerization of the double bond.

In conclusion, the first examples of a *N*-amino 3-aza Cope rearrangement as well as the first *N*-amino-anion 3-aza Cope rearrangement are reported. These occur in good to excellent yields and in short reaction times.



Scheme 3.

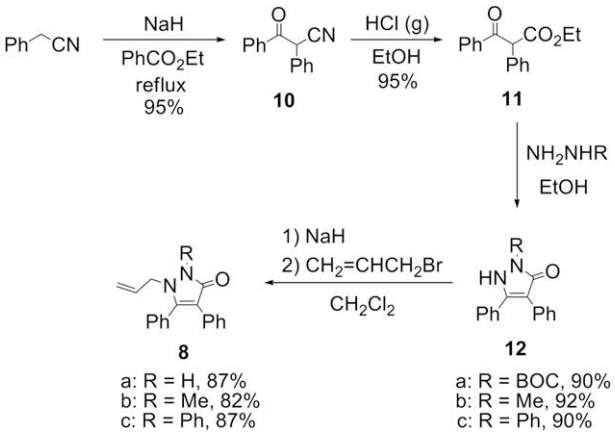


Scheme 2.

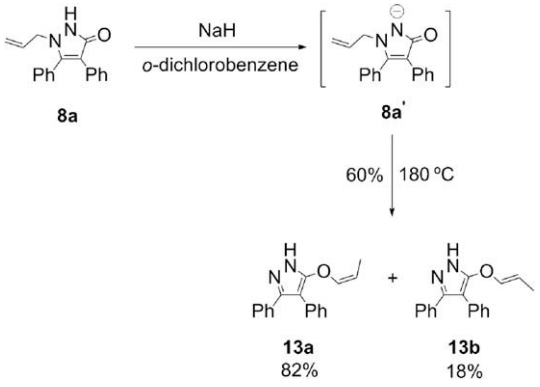
Table 2
Rearrangement of pyrazolones derivatives

No.	**8**	Reaction time (min)	Yield of **9** (%)
1	**a**: R = H	30	20[a]
2	**b**: R = Me	15	92
3	**c**: R = Ph	10	95

[a] Reaction in Ph_2O (259 °C).



Scheme 4.



Scheme 5.

Acknowledgements

We thank Fundação para a Ciência e a Tecnologia (FC&T, Lisbon, Portugal) for partial financial support (Project POCTI/QUI/36456). One of us (P.M.C.G.) is grateful for the award of a fellowship from FC&T.

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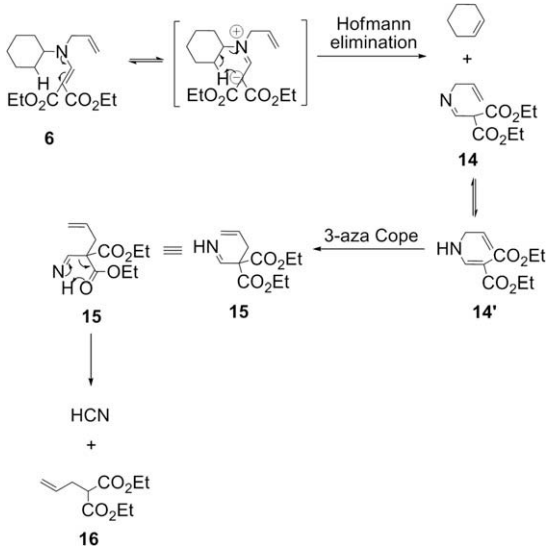
6. *Typical experimental procedure*: A solution 0.14 M of the (*E*)-methyl 3-(1-allyl-2,2-dimethylhydrazinyl) acrylate (**4a**, Table 1, entry 1) in diphenylether (1 ml) was heated under reflux until all the starting materials had been consumed (10 min) (tlc control, silica, *n*-hexane/AcOEt 2:1 as eluent). Evaporation of the solvent under reduced pressure, followed by purification of the residue by ptlc, gave the stable hydrazone (**5a**, Table 1, entry 1), as a light yellow oil (73% yield). Selected spectroscopic data: *Compound* **4a**: IR (neat) 1694 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ δ): 2.45 (6H, s), 3.57 (3H, s), 3.70 (2H, d, J = 5.6 Hz), 4.71 (1H, d, J = 8.7 Hz), 5.18–5.12 (2H, m), 5.73 (1H, m), 7.47 (1H, d, J = 11.8 Hz); EIMS m/z 185 [(M+H)$^+$, 100], 184 (M$^+$, 73), 153 ($C_8H_{13}N_2O^+$, 61), 143 ($C_6H_{11}N_2O^{2+}$, 51). *Compound* **5a**: IR (neat) 1737 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.57–2.42 (2H, m), 2.76 (6H, s), 3.34 (1H, q, J = 7.2 Hz), 3.68 (3H, s), 5.03 (1H, d, J = 10.4 Hz), 5.07 (1H, d, J = 17.1 Hz), 5.75 (1H, m), 6.48 (1H, d, J = 6.8 Hz). ESIMS m/z: 184,12146 ($C_9H_{16}N_2O_4$ require 184,12118).
7. The rearrangement of enamine **6** (Scheme 2b) was accomplished with the formation of allyl diethylmalonate (**16**, 52% yield). The formation of this can be explained by a competitive reaction initiated by a Hofmann elimination affording cyclohexene and the enamine **14'**. This can rearrange to form the imine **15**, which can then liberate HCN affording the allyl diethylmalonate (**16**)



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