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A novel isocyanide based three component reaction†

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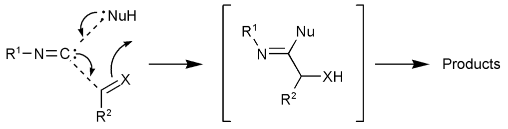
A three component reaction involving an isocyanide, a carboxylic acid and an epoxide or aziridine is described.

Within the last decade, the resurgence of interest in multi-component reactions has been driven, not only because of their inherent atom efficiency and ease of implementation, but also because of their value to the pharmaceutical industry for construction of low molecular weight compound libraries through combinatorial strategies or parallel synthesis.[1–3] Within this reaction class, the unique reactivity profile of the isocyanide functional group[4] has proven to be particularly useful, as summarised in Scheme 1, for both the classical three component Passerini reaction[5] and for the many elegant four component reactions and related processes pioneered by Ugi.[6]

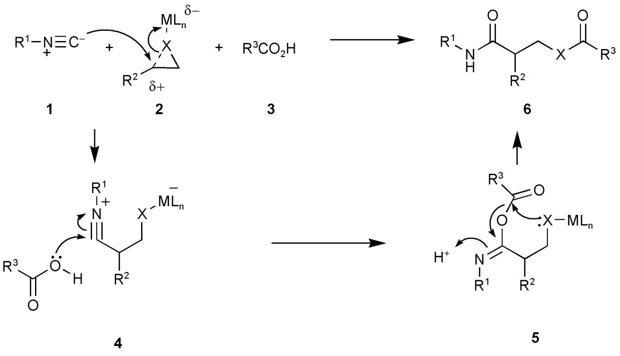
We were intrigued to note however that although many variations of the second nucleophilic component (Nu:) in such reactions have been reported, the carbonyl group or its derived imine or iminium cation has invariably been selected as the electrophilic partner. To the best of out knowledge, an isolated report by Ugi[7] on the reaction of tropylium perchlorate with *tert*-butyl isocyanide in the presence of water to give *N-tert*-butylcycloheptatriene carboxamide provides a rare example of an alternative carbocationic partner.

In view of the above observations we therefore elected to study the behaviour of an epoxide or aziridine (**2**) in a three component reaction with an isocyanide (**1**) and a carboxylic acid (**3**). We reasoned, as shown in Scheme 2, that if capture of the carbocation or incipient carbocation derived *via* assisted S_N1 like ring opening of the three membered ring by the isocyanide was a highly efficient step, then the resultant nitrilium cation (**4**) would undergo nucleophilic attack by 'carboxylate' to give an *O*-acyl imidate (**5**) predisposed towards subsequent migration to the heteroatom of the original three membered ring. In formal terms, the reaction product (**6**) can therefore be viewed as an unusual coupling reaction of an amine *via* its isocyanide derivative with a carboxylic acid with concomitant insertion of a β-hydroxy or β-amino acid unit as a 'linker' and without the necessity of using standard peptidic coupling reagents.



Passerini Reaction: X=O, Nu=RCO_2H
Ugi Reaction: X=NHR, N^+R_2

Scheme 1



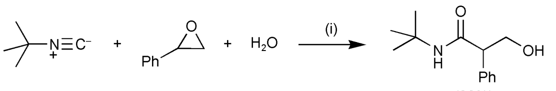
ML_n= Lewis Acid catalyst, X=O, NH

Scheme 2

From the outset of this study we were cognisant of the fact that, in sharp contrast to the ubiquitous S_N2 ring opening of epoxides, the evolution of the incipient carbocation in an S_N1 like ring opening can follow a variety of competing pathways in addition to nucleophilic capture. These include, *inter alia*, hydride transfer, alky (or aryl) migration (leading to ring contraction in cyclic systems) and proton loss. The outcome for any given reaction is therefore critically dependent both on substrate structure and on the nature of the Lewis acid, metal salt or Brønsted acid used to trigger the ring opening reaction.[8–10]

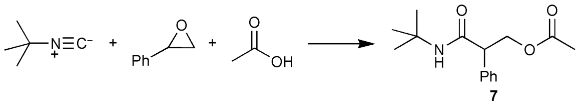
For this reason our initial studies concentrated on the behaviour of the stabilised carbocation derived from styrene oxide, and gratifyingly, for the simple control experiment shown in Scheme 3 with *tert*-butyl isocyanide and water as the second nucleophile, and *para*-toluenesulfonic acid as the catalyst, the desired β-hydroxy carboxamide was isolated in very good yield after chromatography.

However, on directing our attention towards the use of a carboxylic acid as the second nucleophilic component, *para*-toluenesulfonic acid proved to be a much less efficient catalyst, and a wide variety of Lewis acidic metal salts were therefore screened for the prototypical reaction shown in Scheme 4. The results of this study are shown in Table 1 and clearly highlight



(i) catalyst, *para*-toluenesulfonate

Scheme 3



7

Scheme 4

Table 1 Influence of catalyst on the yield of **7**

Catalyst	Isolated Yield of **7** (%)
TsOH	33
ZnX_2	X = Cl 21; X = OTf 63
LiOTf	75
$Cu(OTf)_2$	15
$M(OTf)_3$	M = Sc 35; M = La 33; M = Yb 28

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† Electronic Supplementary Information (ESI) available: experimental and spectroscopic data. See http://www.rsc.org/suppdata/cc/b3/b310962c/

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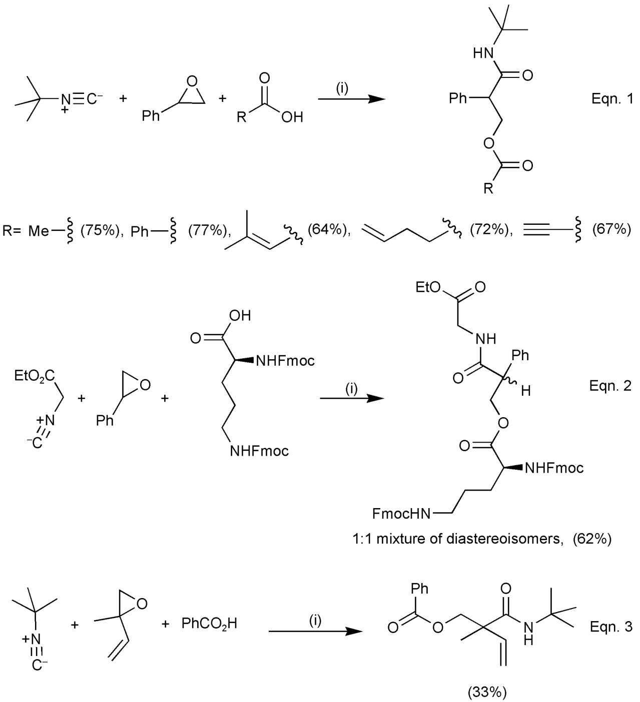
the sensitivity of the reaction to the nature of both the metallic cation and the counterion, with lithium triflate emerging as the catalyst of choice.

A preliminary study of the scope of this reaction in terms of the three components is presented in Scheme 5 and reveals several features of interest. Thus, as indicated in Eqn. 1, aliphatic, aromatic and α,β-unsaturated carboxylic acids can all be used and remote alkene or alkyne functionality is well tolerated. Equation 2 provides an example of the use of a suitably protected amino acid in a coupling reaction with ethyl isocyanoacetate to give a product which can formally be considered as derived from the coupling of glycine ethyl ester with 2-phenyl-3-hydroxypropionic acid followed by esterification using Fmoc protected lysine. The selection of a vinyl epoxide (Eqn. 3) as the oxirane component demonstrates that interception of an allylic cation is also possible in this sequence, albeit that the three component product was formed in lower isolated yield.

The necessity for selection of an epoxide which leads to the formation of a relatively long lived, low energy carbocation is in fact an important caveat. This fact was underscored in an attempted reaction using 1-methylcyclohexene oxide which afforded the Passerini product (**9**), which can be formally derived from the rearranged ring contracted aldehyde (**8**) *via* the pathway shown in Scheme 6.

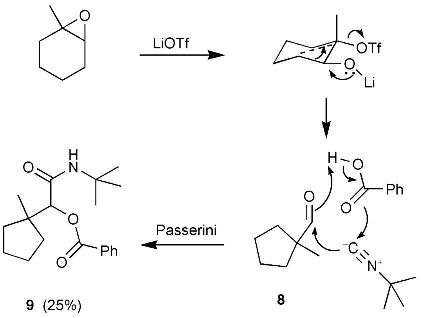
Finally, we have also examined the potential for use of an aziridine in such reactions as demonstrated by the three component sequences outlined in Scheme 7.

In summary, provided that the S_N1 type ring opening of the epoxide or aziridine leads to a low energy cation, the present reaction represents a new, preparatively simple and atom efficient three component reaction which proceeds under mild conditions. Given the wealth of functionalised isocyanides which are readily prepared from the chiral pool of amino acids and carbohydrates,[11] the present reaction may therefore offer considerable potential for the construction of low molecular weight libraries.

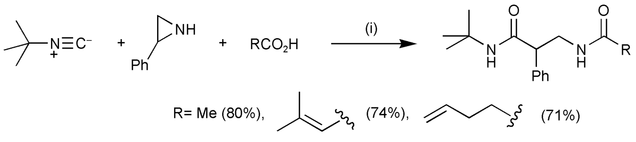


(i) Reagents and conditions: LiOTf (1 eq.), THF, reflux

Scheme 5



Scheme 6



(i) Reagents and conditions: LiOTf (1eq.), THF, reflux

Scheme 7

Notes and references

1 G. H. Posner, *Chem. Rev.*, 1986, **86**, 831.

2 A. Tuch and S. Wallé, Multicomponent Reactions, in *Handbook of Combinatorial Chemistry*, ed. K. C. Nicolaou, R. Hanko and W. Hartwig, Vol. 2, Wiley-VCH, Weinheim, 2002; W. Bannwarth, Combinatorial Chemistry, in *Combinatorial Chemistry – A Practical Approach*, ed. W. Bannwarth and E. Felder, Wiley-VCH, 2000; D. Obrecht and J. M. Villalgorda, Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries, Tetrahedron Organic Chemistry Series Vol. 17, series ed. J. E. Baldwin and R. M. Williams, Pergamon–Elsevier Science, 1998.

3 L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; T. L. Ho, *Tandem Organic Reactions*, Wiley, 1992.

4 For some illustrative isocyanide chemistry see, *inter alia*, R. Neidlein, *Chem. Ber.*, 1964, **97**, 3476; J. Knight and P. J. Parsons, *J. Chem. Soc., Chem. Commun.*, 1987, 189; Y. Ito, H. Kato, H. Imai and T. Saegusa, *J. Org. Chem.*, 1982, **47**, 741; J. H. Rigby, M. Qabar, G. Ahmed and R. C. Hughes, *Tetrahedron*, 1993, **49**, 10219.

5 M. Passerini and G. Ragni, *Gazz. Chim. Ital.*, 1931, **61**, 964.

6 A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3169; I. Ugi, *J. Prakt. Chem.*, 1997, **339**, 499; I. Ugi and C. Steinbrückner, *Chem. Ber.*, 1961, **94**, 734; I. Ugi and C. Steinbrückner, *Chem. Ber.*, 1959, **71**, 386; I. Ugi and K. Rosendahl, *Chem. Ber.*, 1961, **94**, 2233.

7 I. Ugi, W. Betz and K. Offermann, *Chem. Ber.*, 1961, **97**, 3008.

8 R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 737.

9 E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421.

10 D. J. Morgans Jr. and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 335.

11 For some representative examples see, *inter alia*, D. H. R. Barton, G. Bringmann and W. B. Motherwell, *Synthesis*, 1980, 68; D. H. R. Barton, G. Bringmann and W. B. Motherwell, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2665.