A new multicomponent reaction of nitro compounds with isocyanides

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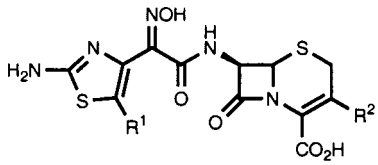
The first multicomponent reaction between nitro compounds, isocyanides and acylating agents is described, providing an original route to α-oximinoamides.

α-Oximinoamides form a class of compounds with useful pharmaceutical applications as shown by the structures of cephalosporin **1** and β-lactamase inhibitor **2**.[1] Following our efforts towards finding new applications of isocyanides in synthesis,[2] we wish to report a straightforward synthesis of α-oximinoamides by the interaction of isocyanides with nitro compounds.



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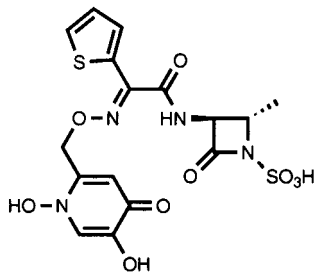

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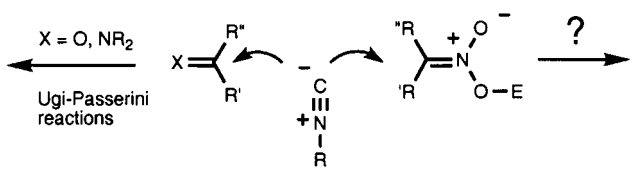
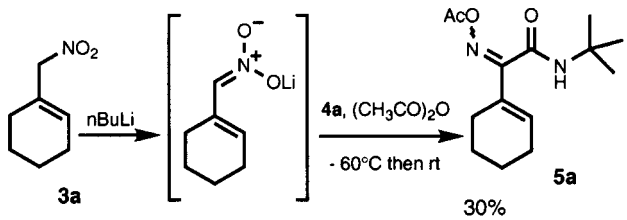
Most applications of nitro compounds in synthesis take advantage of easy proton abstraction under basic conditions to form nitronate anions followed by coupling with an electrophile.[3] Nucleophilic attack by carbon nucleophiles on the carbon of the nitro group are more rare. Water adds to nitro compounds following their conversion into the tautomeric nitronic acids, leading to their efficient transformation into ketones and aldehydes (Nef reaction).[4] The extension of the Nef reaction to carbon nucleophiles has probably been hampered by the reported instability of nitronic acid derivatives.[5] Besides some useful [3 + 2] cycloaddition of nitronates under acid catalysis,[6] this approach has been mainly exploited by Seebach *et al.*, giving average to good yields of ketoximes from primary nitro compounds and alkyllithiums.[7]

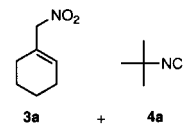
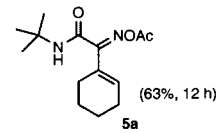
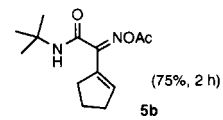
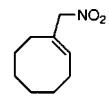
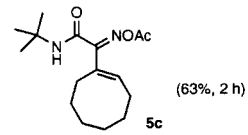
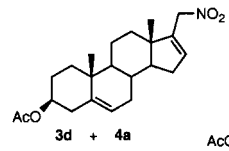
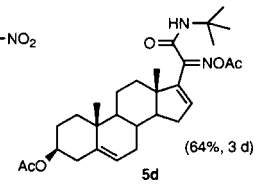
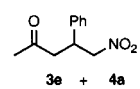
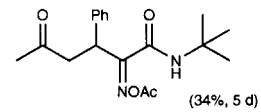
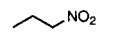
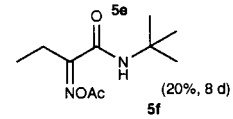
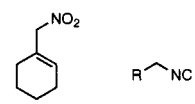
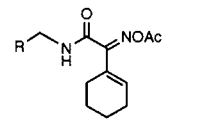
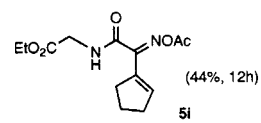


Scheme 1 Nucleophilic attack of isocyanides on carbonyl derivatives.

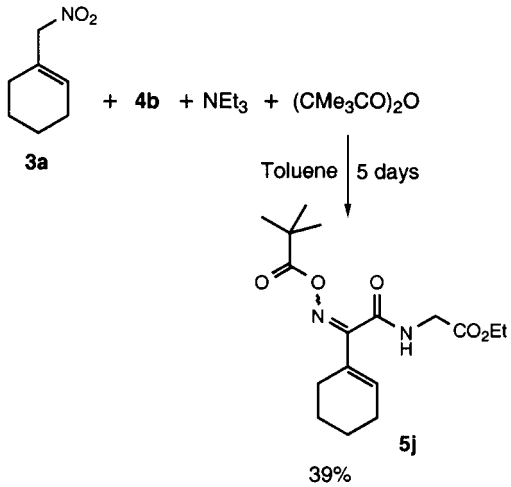


Scheme 2 Addition of *tert*-butyl isocyanide **4a** on the nitronate derived from **3a**.

Table 1 Products isolated after isocyanide addition to nitro compounds[a]

Starting nitro and isocyano compounds	Product (yield, time)
 **3a** + **4a**	 (63%, 12 h) **5a**
 **3b** + **4a**	 (75%, 2 h) **5b**
 **3c** + **4a**	 (63%, 2 h) **5c**
 **3d** + **4a**	 (64%, 3 d) **5d**
 **3e** + **4a**	 (34%, 5 d) **5e**
 **3f** + **4a**	 (20%, 8 d) **5f**
 **3a** + **4b** R = CO_2Et **4c** R = 4-MeOPh	 **5g** R = CO_2Et (30%, 2 d) **5h** R = 4-MeOPh (51%, 24 h)
 **3b** + **4b**	 (44%, 12h) **5i**

[a] Ref. 11.



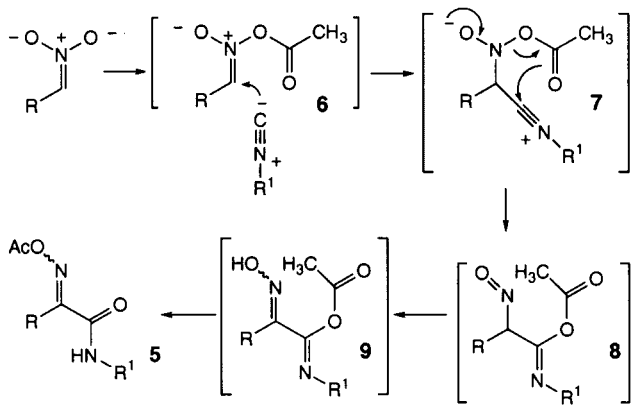
Scheme 3 Addition of isocyanide **4a** to nitro derivative **3a** under pivalic anhydride activation.

The Ugi–Passerini reactions[8] exploit the nucleophilic properties of isocyanides towards carbonyl derivatives; a similar reaction can be envisaged with nitronic acids as shown in Scheme 1.

Keeping in mind the sensitivity of nitronic acid derivatives and their ability to form nitrile oxides,[5] we first examined and reported[9] the behaviour of isocyanides in the presence of NEt_3, primary nitro compounds and butyl isocyanate under conditions propicious for nitrile oxide formation. Under such conditions, the primary nitro compound is cleanly converted into a nitrile by oxygen transfer to the isocyanide.

To avoid nitrile oxide formation, we decided to generate the *O*-acyl nitronate at low temperatures in the presence of the isocyanide by analogy to the addition of organometallics to silyl and acyl nitronate.[7,10] Preliminary experiments were encouraging as a 30% yield of the α-oximinoamide **5a** was obtained after reaction of nitro derivative **3a** with butyllithium, acetic acid anhydride and *tert*-butyl isocyanide **4a** (Scheme 2). However all our attempts to raise this yield through changes in reactants, temperature and order of addition did not meet with success.

Our problems may stem from the ambiphilic nature of nitronic acid derivatives which may compete as nucleophiles with the isocyanide; a slow generation of the reactive *O*-acyl nitronate in the presence of the isocyanide could alleviate this problem. In our conversion of nitro compounds into nitriles,[9] fast dimerisation of nitrile oxide was suppressed under such conditions: slow generation of nitrile oxide through nitronate formation using a tertiary amine in toluene. Indeed, a remarkable increase in yield (63%) was observed when a solution of nitro compound **3a** (1 M), NEt_3 (1.1 equiv.), acetic acid anhydride (1.1 equiv.) and isocyanide **4a** was left to react at room temperature for a few hours. Various nitro compounds **3** and isocyanides **4** were tested in this new multicomponent reaction, giving moderate to good yields of α-acyloximinoamide **5** (Table 1).



Scheme 4 Possible mechanism for the formation of amides **5**.

As observed for nitrile formation, best yields were obtained with allylic nitro derivatives prone to easy base deprotonation. For aliphatic nitro compounds, the yield can however be raised by a proper selection of the reagents, the formation of **5f** was thus enhanced up to 60% yield by changing from NEt_3 to the more basic DBU. The synthetic potential of this reaction can easily be extended by a change in the starting carboxylic acid (Scheme 3). A significant decrease in yield was observed with isocyanides possessing electron withdrawing groups. Even though yields are modest, it represents nevertheless a very straightforward preparation of complex dipeptide analogues **5g**, **5i** and **5j**. A possible mechanism for this new reaction is depicted in Scheme 4. The acid-base equilibrium between the nitro compound and its nitronate conjugate base is slowly displaced with acetic acid anhydride to give the *O*-acyl nitronate **6**. The latter, though highly unstable at room temperature, is trapped by the isocyanide to give the putative species **7**–**9** through nitroso formation and acylation of the tautomeric oxime.

In conclusion, we have disclosed in this study, the first three-component reaction involving the addition of isocyanides to nitro compounds. This reaction enables a fast preparation of complex peptide analogues from readily available nitro derivatives; it could find application in total synthesis as well as in combinatorial chemistry. Efforts to increase the yield by a proper selection of reagents and solvents are under way in our group.

Notes and references

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8 I. Ugi, *Isonitrile Chemistry*, Academic Press, New York, 1971.
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11 A typical experimental procedure is as follows: to a solution of nitro compound (2 mmol) in toluene (2 ml) were added NEt_3 (2.2 mmol), acetic anhydride (2.2 mmol) and isocyanide (3 mmol). The reaction was stirred at room temperature under an inert atmosphere until completion (a few hours to a few days for aliphatic nitro compounds); evaporation of the solvent and chromatography on silica finally furnished the desired product.

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