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A Multicomponent Reaction Towards *N*-(Cyanomethyl)amides

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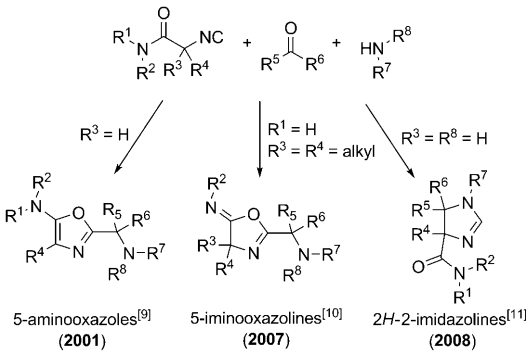
Multicomponent reactions (MCRs)[1] have emerged as useful tools in diversity-oriented synthesis (DOS).[2] Although a number of substituents can be varied over a broad range, MCRs often access products of one specific scaffold, limiting the overall chemical diversity. To overcome this, MCRs have been combined with other types of reactions such as Diels–Alder reactions,[3] click chemistry,[4] and cyclization strategies[5] to generate structural diversity and a high degree of complexity in a minimal number of reaction steps. Our group contributed in this field by trapping 1-azadienes,[6] generated by the three-component reaction (3-CR) between phosphonates, nitriles and aldehydes,[7] with various reactants resulting in novel 4-CRs for a variety of heterocyclic scaffolds.[8]

Recently, we, and also others, reported the selective formation of different products based on a single combination of reactants. In a reaction between α-isocyano amides, amines and carbonyl components, the outcome of the reaction can be directed depending on subtle changes in the substrates and conditions. First, the synthesis of 5-aminooxazoles starting from aldehydes or ketones, primary or secondary amines and tertiary α-isocyano amides ($R^1=R^2=$alkyl, $R^3=H$, Scheme 1) was reported.[9] Later, a variation of this 3-CR was reported using secondary α,α-disubstituted isocyano amides ($R^1=H$, $R^2=R^3=R^4=$alkyl) to yield 5-iminooxazolines.[10] The same reaction conditions as for the 5-aminooxazoles could be used, which, due to the absence of α-protons on the isocyano amide, yielded the non-aromatized product. In 2008, we reported a third scaffold from this 3-CR.[11] Herein α-acidic isocyano amides ($R^3=H$), primary amines ($R^8=H$), and carbonyl components react in the presence of 2 mol% AgOAc (or CuI) to give 2*H*-2-imidazolines.[11,12] Careful tuning of the reaction conditions led to a procedure to control and direct the outcome of this MCR to either oxazoles or 2*H*-2-imidazolines, resulting in considerable chemical diversity for a single combination of reagents. In this way, at least six diversity points in three distinct scaffolds are covered.



Scheme 1. A diverse set of scaffolds from the MCR between α-isocyano amides, amines and carbonyl compounds.

In light of our ongoing interest in the application of α-acidic isocyanides in MCRs, we used α-isocyano acetamide (**1a**), cyclohexanone (**2a**) and morpholine (**3a**) in equimolar amounts under the conditions optimized for the 5-aminooxazole MCR (MeOH, $MgSO_4$ (drying agent), 60 °C, 5 h).[11] Rather than the expected primary 5-aminooxazole we isolated **4a** (Scheme 2).

These types of *N*-(cyanomethyl)amides show diverse biological activities and existing syntheses are certainly not straightforward.[13] The unexpected formation of **4a** can be rationalized by the attack of the isocyanide terminal C atom on the in situ generated iminium ion followed by cyclization

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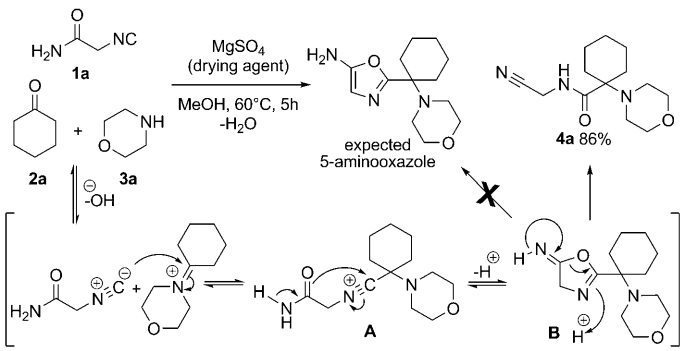
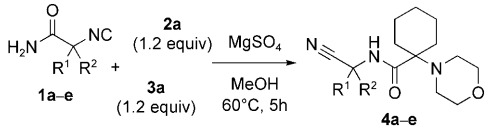
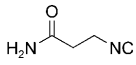
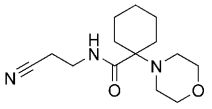


Scheme 2. Suggested mechanism for the formation of **4a**.

and proton abstraction to form 5-iminooxazoline intermediate **B** (Scheme 2). Intermediate **B** could, in principle, undergo tautomerization to form the aromatic primary 5-aminooxazole, but instead, proton abstraction at the exocyclic imine nitrogen and subsequent ring opening (via a rearrangement previously reported for related compounds[14]) occurs to give **4a**. The isolated yield of **4a** could be increased to 93% by using 1.2 equiv of the amine and ketone components (Table 1, entry 1) and the scope of compatible

Table 1. Scope of isocyanides (**1**) using cyclohexanone (**2a**) and morpholine (**3a**) for the MCR towards **4**.



Entry	R^1	R^2	Product	Yield [%]
1	H	H	**4a**	93
2	H	Et	**4b**	93
3	H	*i*Pr	**4c**	87
4	H	Ph	**4d**	64
5	$-(CH_2)_5-$		**4e**	81
6				55 (18 h)

primary α-isocyano amides was quite general. The R^2 substituent can be varied over a broad range (H, Et, *i*Pr, and Ph) affording the corresponding *N*-(cyanomethyl)amides in 64–93% isolated yield (entries 1–4). The structure of product **4d** was confirmed by X-ray crystallography (Figure 1). Even the sterically demanding α,α-dialkyl isocyanide **1e** and the β-isocyano amide **5** proved successful substrates (entries 5 and 6).

The amine and carbonyl components could also be varied considerably (Figure 2). Aromatic amines and aldehydes could be used (**4f** and **4i**, respectively) and also bulky components gave the corresponding *N*-(cyanomethyl)amides in high yields (**4g–i**, **m**). However, when the steric bulk becomes too large, the product is not obtained (**4l**, **n**), probably due to sluggish imine formation or steric hindrance in the attack of the isocyanide.

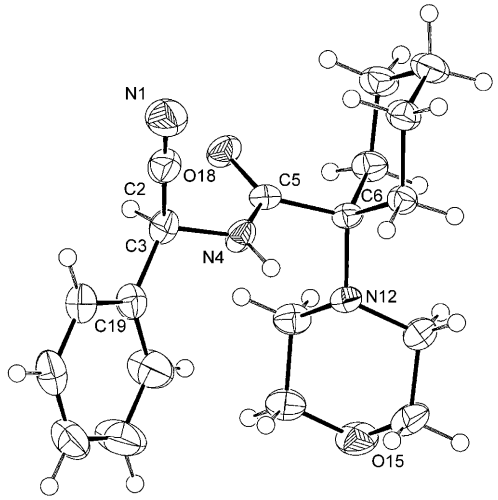


Figure 1. Molecular structure of **4d** in the crystal. Displacement ellipsoids are drawn at 50% probability level. Only the *S* enantiomer of this racemic compound is shown.

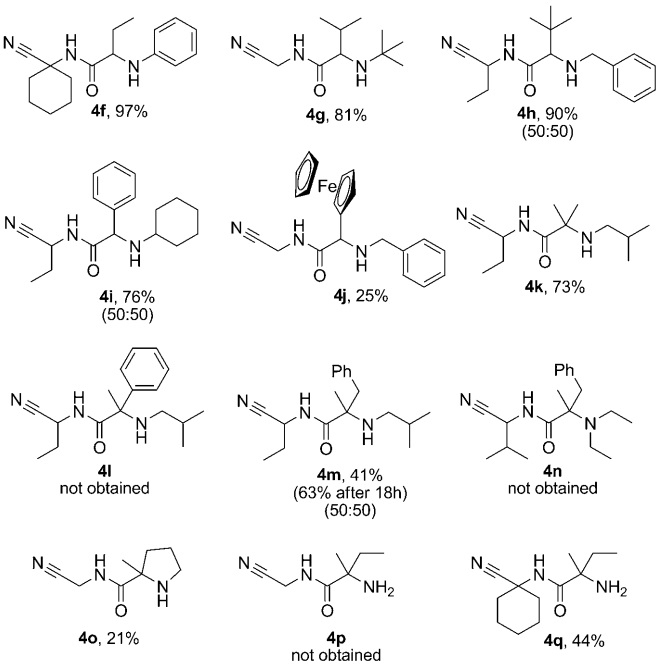
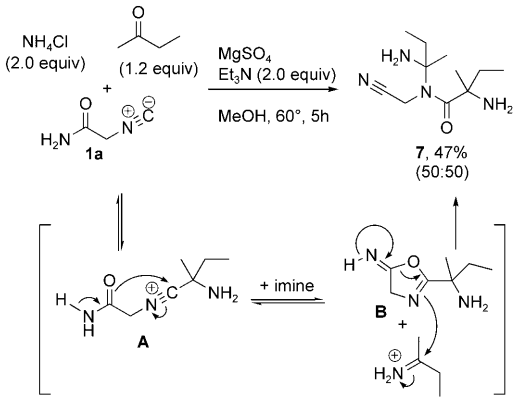


Figure 2. Variation of amine and carbonyl components.

Interestingly, by using isocyanide **1a**, butanone, and ammonia **4p** was not obtained. Instead, compound **7** was isolated in 47% yield (Scheme 3). The formation of **7** presumably proceeds via a similar mechanism leading to **4**. However, in the rearrangement, the oxazoline N atom of **B** may attack a second equivalent of imine due to the reduced steric repulsion with these small reactants (Scheme 3). This is supported by the reaction of the same imine with the more sterically hindered isocyanide **1e**. In this case, the increased steric



Scheme 3. Proposed mechanism for the formation of **7**.

bulk on **B** prevents attack on a second equivalent of imine and **4q** is formed instead (44%, Figure 2).

Many functional groups are tolerated in this new MCR toward *N*-(cyanomethyl)amides, including alkynes (**4r**, Figure 3), alcohols (**4s**), furans (**4t**) and even additional primary amide (**4u**) and isocyanide (**4v**) groups. Functional groups can be introduced on all accessible sites of the *N*-(cyanomethyl)amide making in situ follow-up (multicomponent) reactions feasible.

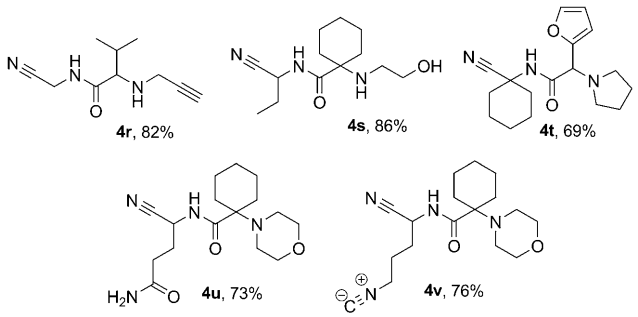
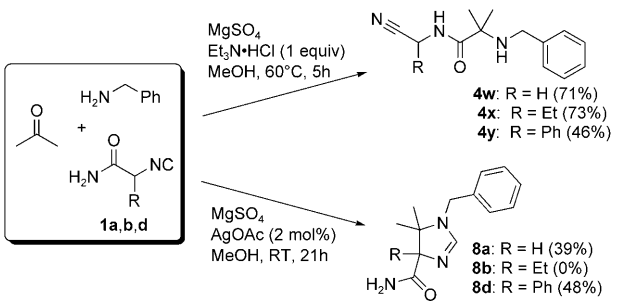


Figure 3. Functional group tolerance.

As reported by us earlier for tertiary α-isocyano amides,[11] the outcome of the MCR can be directed toward 2*H*-2-imidazolines by slightly changing the reaction conditions (Scheme 4). Addition of only 2 mol% AgOAc in combination with the slow addition of the isocyanide resulted in the selective formation of 2-imidazolines **8a** and **8d**. As reported, attempts to isolate the 2-imidazoline starting from α-alkyl substituted isocyano amides (such as **1b**) failed due to the increased pK_a of the α-proton.[11]



Scheme 4. Directing the MCR towards **4** or **8**.

In conclusion, we have developed a fourth MCR starting from α-isocyano amides, amines and carbonyl components. The resulting *N*-(cyanomethyl)amides can be isolated in moderate to excellent yield using a wide range of primary and secondary amines as well as aldehydes and ketones. In addition to the broad substrate scope of the reaction, a number of functional groups (including additional amide and isonitrile groups) are tolerated, thus eliminating the need for protective groups and allowing direct post-modification. Finally, we were able to direct the reaction outcome toward 2*H*-2-imidazolines by slight modification of the reaction conditions.

Experimental Section

Synthesis of *N*-(cyanomethyl)amides 4a–y, 6, and 7: Unless stated otherwise, the corresponding primary(α-isocyano)amide **1a–g** (1.0 mmol), aldehyde or ketone (1.2 mmol), and amine (1.2 mmol) were stirred in MeOH (5 mL) in the presence of $MgSO_4$ for 5 h at 60 °C. Water (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3× 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated, and the resulting *N*-(cyanomethyl)amides were purified by column chromatography.

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