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A Novel Three-Component Reaction toward Dihydrooxazolopyridines

Rachel Scheffelaar,[†] Monica Paravidino,[†] Daan Muilwijk,[†] Martin Lutz,[‡] Anthony L. Spek,[‡] Frans J. J. de Kanter,[†] Romano V. A. Orru,*[,†] and Eelco Ruijter[†]

Department of Chemistry and Pharmaceutical Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands, and Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands

orru@few.vu.nl

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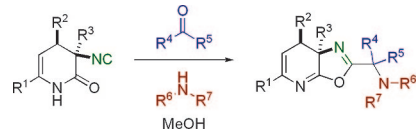
ABSTRACT



Isocyano dihydropyridones accessible via a recently reported multicomponent reaction react with aldehydes and amines to afford dihydrooxazolopyridines in high yield. The scope and limitations of this novel multicomponent reaction were investigated. The efficient combination of two highly variable multicomponent reactions allows the construction of a very broad range of dihydrooxazolopyridines, an unexplored class of bicyclic compounds. The implications of the observed reactivity profile for the mechanism of this multicomponent reaction are discussed.

Multicomponent reactions (MCRs) have gained considerable popularity in the synthetic community. They provide efficient access to complex molecules from readily available starting materials.[1] They also form an ideal platform for rapid generation of both complexity and diversity in a collection of compounds with predefined functionality, e.g., ligands for catalysis or bioactive compounds. This may be achieved by combining MCRs with other common organic reactions or even with additional yet different MCRs, thus allowing coverage of large portions of chemical space. Moreover, MCRs are ideal synthetic tools to generate multiple molecular scaffolds from the same starting materials or intermediates and are therefore considered to be most effective to increase structural or skeletal diversity. Within the concept of diversity-oriented synthesis (DOS), this generation of scaffold diversity is one of the major hurdles to overcome.[2]

We have contributed to this area by the rational design of modular reaction sequences based on a common intermediate, a 1-azadiene derived from a one-pot reaction of phosphonates, nitriles, and aldehydes (Figure 1).[3−7] This versatile intermediate can be trapped in situ by a fourth component to afford various heterocyclic scaffolds (**1**−**5**, Figure 1).[4,5] Relevant to this communication is the application of this

[†] Vrije Universiteit Amsterdam.
[‡] Utrecht University.

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strategy to arrive at 3,4-dihydropyridin-2-ones (DHP-2-ones, **1**).[5]

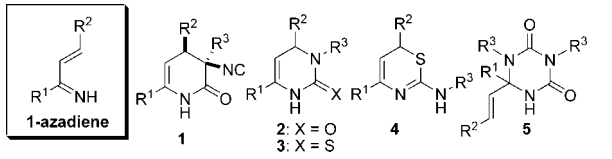
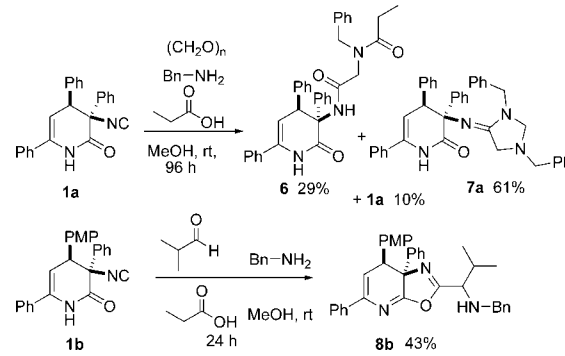


Figure 1. Scaffold diversity from our 1-azadiene based MCRs.

In this case, the normally rather reactive isocyanide group[1,6] is retained in the DHP-2-one MCR products. This allows the combination with a second complexity-generating reaction, as we demonstrated by the (one-pot) combination of this four-component reaction (4CR) with the well-known Passerini 3CR leading to a 6CR for conformationally constrained depsipeptides.[7] To further explore the synthetic potential of this concept, we turned our attention to the combination of our 4CR for isocyano DHP-2-ones **1** with another isonitrile-based MCR, the Ugi 4CR.[1a,e,8] First, the Ugi reaction of **1a**, paraformaldehyde, benzylamine, and propionic acid was studied. Indeed, Ugi product **6** was obtained, albeit in moderate yield (29%), together with iminoimidazolidine **7a** (61%, Scheme 1) and unreacted **1a** (10%).[9] We then studied the combination of **1b** with isobutyraldehyde, benzylamine, and propionic acid. This did not afford the expected Ugi product nor the corresponding iminoimidazolidine. Instead, a product was isolated that clearly did not incorporate the propionic acid. Thorough spectroscopic analysis led to dihydrooxazolopyridine (DHOP) **8b** (Scheme 1, 43%) as the most plausible structure, which is the result of the condensation between **1b** and the imine derived from the aldehyde and amine components. It should be noted that *N*-alkylated derivatives of **1** were successfully combined with aldehydes, amines, and carboxylic acids to afford a diverse set of Ugi products.[9a] X-ray crystal structure determination of **8k** (Table 1, entry 11) confirmed the unprecedented heterobicyclic DHOP structure[10] (Figure 2) as the product of this new 3CR.

Oxazolopyridines display anti-inflammatory,[11] antibacterial,[12] antipyretic, and analgesic properties.[13] Although not aromatic, the DHOPs are fairly flat bicyclic ring systems with R^2 and R^3 substituents in a *trans*-pseudodiaxial orientation (as is evident from the crystal structure of **8k**) and

Scheme 1. Initial Results of Isonitrile-Based MCRs Using **1**



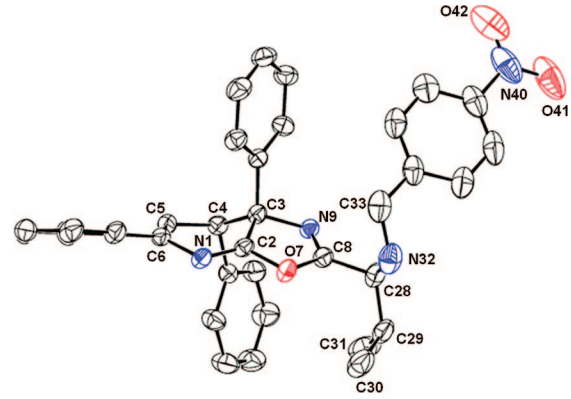


Figure 2. Displacement ellipsoid plot of **8k**. Drawn at 50% probability level. The compound is crystallized as a racemate in the centrosymmetric space group *P*1.

can therefore be considered as promising alternatives for the oxazolopyridines. The novelty and interesting products of this MCR spurred us to find optimal conditions and investigate the scope of the reaction. The absence of the carboxylic acid apparently excludes several side reactions, since the yield of **8b** increased considerably when **1b** was treated with only isobutyraldehyde and benzylamine in MeOH at room temperature (cf. Scheme 1 and entry 2, Table 1). Formation of **8b** proceeded more efficiently in the polar protic solvent MeOH (73%) than in aprotic THF (49%) or less polar CH_2Cl_2 (29%). The 3CR performs optimally when

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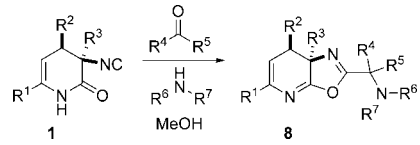
Table 1. Scope Study of the New 3CR towards Dihydrooxazolopyridines (DHOPs)[a]

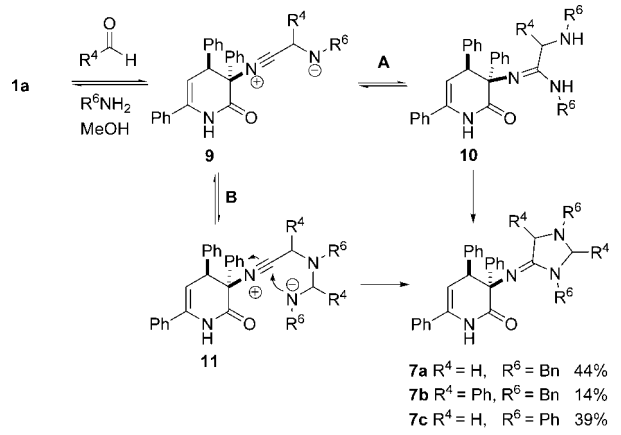


entry	DHP-one	R^1	R^2	R^3	R^4	R^5	R^6	R^7	DHOP	yield (%)
1	**1a**	Ph	Ph	Ph	*i*Pr	H	Bn	H	**8a**	81
2	**1b**	Ph	PMP	Ph	*i*Pr	H	Bn	H	**8b**	73
3	**1c**	Ph	PCP	Ph	*i*Pr	H	Bn	H	**8c**	76
4	**1d**	Ph	cyclohexen-1-yl	Ph	*t*Bu	H	Bn	H	**8d**	89
5	**1e**	Ph	Ph	PCP	*i*Pr	H	Bn	H	**8e**	77
6	**1e**	Ph	Ph	PCP	cyclohexyl	H	Bn	H	**8f**	77
7	**1e**	Ph	Ph	PCP	*i*Pr	H	*n*Bu	H	**8g**	77
8	**1e**	Ph	Ph	PCP	*i*Pr	H	Ph	H	**8h**	77
9	**1f**	iPr	PMP	Ph	*i*Pr	H	Bn	H	**8i**	100
10	**1f**	iPr	PMP	Ph	*i*Pr	H	Ph	H	**8j**	75
11	**1a**	Ph	Ph	Ph	*i*Pr	H	PNB	H	**8k**	89
12	**1a**	Ph	Ph	Ph	Me	Me	Bn	H	**8l**	34[b] (62)[c]
13	**1a**	Ph	Ph	Ph	Ph	H	Bn	H	**8m**	*d*
14	**1c**	Ph	PCP	Ph	Ph	H	*n*Bu	H	**8n**	*e*
15	**1a**	Ph	Ph	Ph	H	H	Bn	H	**8o**	*f*
16	**1a**	Ph	Ph	Ph	H	H	Ph	H	**8p**	*g*
17	**1c**	Ph	PCP	Ph	*t*Bu	H	-$(CH_2)_2$-O-$(CH_2)_2$-		**8q**	45[h] (62)[i]
18	**1c**	Ph	PCP	Ph	*i*Pr	H	-$(CH_2)_2$-O-$(CH_2)_2$-		**8r**	83

[a] Generally, the reactions were carried out in a homogeneous methanolic solution of **1** (0.06−0.68 M), aldehyde, and amine in a 1:1.1:1.1 ratio; 1:1 mixtures of diastereomers are isolated (except for **8l**). [b] 45% of **1a** was recovered. [c] Yield based on recovered **1a**. [d] Formation of **7b** (14%) was accompanied by at least four other unidentified products. [e] 79% of **1c** was recovered. [f] 44% of **7a** was isolated. [g] 39% of **7c** together with 55% of **1a** was isolated. [h] 27% of **1c** was recovered. [i] Yield based on recovered **1c**. PMP = *p*-methoxyphenyl, PNP = *p*-nitrophenyl, PCP = *p*-chlorophenyl, PNB = *p*-nitrobenzyl.

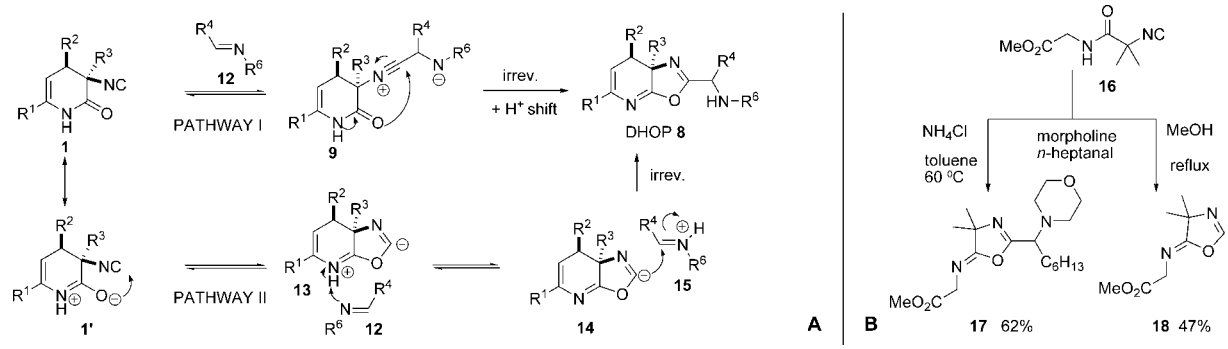
the inputs are homogeneously mixed in MeOH at room temperature with a slight excess of the amine and aldehyde relative to the DHP-2-one. Under these optimized conditions the scope of the 3CR for DHOPs **8** was further explored (Table 1). Six DHP-2-ones **1a**−**1f** were successfully combined with various aldehydes and amines to afford a series of DHOPs **8** in good to excellent yield (entries 1−12, 17, and 18). Stereochemical induction was not observed and typically inseparable ∼1:1 mixtures of diastereoisomers were isolated. In general, the 3CR reaches full conversion in 1−5 days, but additional aldehyde and amine may be added to accelerate the reaction. A wide range of different aliphatic and aromatic primary amines were tolerated in the 3CR (entries 1−11) and the corresponding DHOPs **8a**−**8k** were obtained efficiently. The use of secondary amines is also allowed, even combined with very hindered aldehydes (entries 17 and 18). The choice of the carbonyl compound is more crucial. The use of aliphatic aldehydes generally results in efficient DHOP formation (entries 1−11). Even the use of acetone in combination with **1a** and benzylamine (entry 12) afforded the corresponding DHOP **8l**. The increased steric constraints may account for the somewhat lower yields in this case. Benzaldehyde and paraformaldehyde (entries 13−16) are less efficient inputs in this 3CR. In these cases, iminoimidazolidines **7a**−**7c** were isolated in 14−44%. As reported previously, these are possibly formed via the α-amino amidines **10** (Scheme 2, pathway A).[9b] Imine formation is a reversible process, making formation of **7** (via **10**) feasible. However, neither application of a drying agent (molecular sieves), nor substitution of MeOH by trifluoroethanol as solvent, nor heating the mixture to reflux proved beneficial for DHOP formation. A second reasonable pathway for the formation of **7** is the condensation of a second imine to intermediate **9** and subsequent cyclization of **11** (Scheme 2, Pathway B).

Scheme 2. Formation of Iminoimidazolidine Side Products



The 3CR toward DHOPs **8** may be rationalized by the two pathways depicted in Scheme 3A. Pathway I involves

Scheme 3. (A) Possible Pathways for the 3CR in MeOH towards DHOPs **8** and (B) Iminooxazolines Reported by Zhu et al.[14]



initial attack of the isonitrile carbon in **1** to the imine **12** forming dipolar intermediate **9**, followed by attack of the nucleophilic amide oxygen atom and proton transfer. In pathway II, the resonance structure **1′** initiates formation of the DHOP bicyclic core **13**. Subsequent proton transfer to the imine **12** and attack of the oxazolide nucleophile **14** to the resulting iminium ion **15** accounts for formation of **8**. Formation of iminoimidazolidines **7** presumably involves intermediate **9**, which supports pathway I. Subsequent cyclization of **9** to give **8** should be fast and irreversible, at least faster than attack of a carboxylate since no Ugi product was observed when a carboxylic acid is present. Recently, Zhu et al. rationalized a 3CR of α-isocyanoacetamides, aldehydes, and amines to afford 5-iminooxazolines **17**,[14] by a mechanism similar to pathway I (Scheme 3B).

Other observations are in favor of pathway II. For example the use of paraformaldehyde in the Ugi reaction resulted in a slow formation of **6** and **7a** (96 h, Scheme 1), while the same reaction with the *N*-alkylated analog resulted in much faster (22 h) quantitative formation of the Ugi product.[9] This may indicate that the isonitrile moiety is less accessible, caused by an equilibium of **1** and **13/14** in MeOH. Although efforts to trap intermediate **14** by stirring **1** in MeOH in the absence of imine did not result in the isolation of 2*H*-DHOP, Zhu et al. observed a similar conversion of their α-isocyanoacetamide **16** to 2*H*-2-oxazoline **18** in MeOH (Scheme 3B).[14] Finally, DHOP formation was never observed in Passerini reactions of **1**.[7] Most likely the charged DHOP intermediate **13** is not formed in the less polar DCM. Moreover, aldehydes are much poorer electrophiles than iminium ions, making attack of **14** less favorable.

The experimental support is not conclusive in favor of one specific pathway (I or II). Moreover, none of the presented pathways can explain why DHOPs **8** are not formed with benzaldehyde and formaldehyde as the carbonyl inputs. More detailed mechanistic studies will be required.

In summary, combination of our 1-azadiene based 4CR for DHP-2-ones and the Ugi 4CR led to the serendipitous discovery of a novel three-component condensation affording dihydrooxazolopyridines (DHOPs) in high yield. This interesting new scaffold has high potential for drug discovery, which will be further investigated in the future.

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Supporting Information Available: Detailed experimental methods and complete characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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