## Multicomponent Reactions

## The Efficient One-Pot Reaction of up to Eight Components by the Union of Multicomponent Reactions\*\*

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The development of synthetic methods has advanced enormously in the past decades. At present, chemists can design and prepare almost any type of molecule. The typical approach for the synthesis of (complex) molecules with predefined properties is, however, still characterized by rather inefficient step-by-step reaction sequences. The greatest challenge for synthetic chemists is therefore the improvement of overall efficiency by using atom-, step-, and energyeconomic procedures that proceed with high yield and selectivity.<sup>[1,2]</sup> This goal can be achieved by focusing on bond construction and functional-group compatibility in the development of new reaction types. Multicomponent reactions (MCRs)<sup>[3]</sup> are important tools for the accomplishment of this goal as they inherently involve the formation of several bonds in one operation. As such, MCRs are convergent stepefficient procedures that can take place with remarkably high atom economy<sup>[1a]</sup> and E factors,<sup>[2]</sup> by reducing the number of functional-group manipulations and thus avoiding the use of protecting groups.

Synthetic efficiency can be further improved by combining more than one MCR. Central to this concept of the union of MCRs<sup>[4,5]</sup> is the orthogonal reactivity of functional groups, which can be combined in one molecule to allow the union of different reactions if their reactivity is fully independent (orthogonal). Such strategies avoid the use of protective groups and increase efficiency in organic synthesis.

The most straightforward approach to such combinations is the incorporation of a functional group in one of the inputs of the primary MCR that does not participate in the reaction, but does react as one of the components in a secondary MCR (Figure 1). In an ideal case, both reactions are combined in one pot to create a higher-order MCR. Although there are several reports of combinations of MCRs in the literature, the true one-pot combination (union of MCRs<sup>[4]</sup> first introduced by the research group of Ugi<sup>[5]</sup>) is generally not possible

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Figure 1. Combination (or union) of MCRs.

because: 1) the experimental procedure limits the scope in substrate inputs, 2) additional (de)protection steps are required, and 3) solvent incompatibilities mean that the solvent must be changed between subsequent reaction steps. Consequently, one-pot sequences of MCRs have remained limited to isolated examples by Ugi and co-workers,<sup>[5,6]</sup> Portlock and co-workers,<sup>[7]</sup> and our research group.<sup>[8]</sup>

We report herein a novel approach that combines two or more MCRs in one pot to achieve higher-order MCRs with unprecedented possibilities for complexity generation and diversification. Our strategy is based on two recently reported MCRs that display extraordinary functional-group and solvent compatibilities and lead to 2*H*-2-imidazolines<sup>[9]</sup> and *N*-(cyanomethyl)amides,<sup>[10]</sup> respectively.

In an initial approach, we focused on the introduction of a carboxylic acid function in the 2*H*-2-imidazoline produced by the primary MCR using an amino acid as one of the starting materials. Thus, reaction of isocyanide **1**, acetone, and sodium glycinate (**2**)<sup>[11]</sup> led to a clean conversion to form intermediate **A** (Scheme 1). After protonation of the intermediate carboxylate **A** (methanolic HCl, one equivalent), a one-pot combination with *i*PrCHO, *n*-propylamine, and *t*BuNC in an Ugi  $4CR^{[3g]}$  led to the isolation of **3a** in 38% yield. The yield could be improved to 62% by using benzylamine instead of *n*-propylamine, which is excellent when considering the number



**Scheme 1.** Union of the MCR for 2H-2-imidazolines and the Ugi 4CR with sodium glycinate. M.S. = molecular sieves.

5856

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of bond formations. In fact, the yield per bond formation is 93%. Only a slight excess is required for any of the inputs ( $\leq$ 1.2 equivalents) to achieve excellent conversions. Moreover, this six-component approach allows variation at no less than nine positions in a single reaction step.

We subsequently investigated the possibility of attaching a carboxylic acid function to the 2-imidazoline scaffold through the carbonyl component. Isocyanide **4**, levulinic acid (**5**), and amines **6a**-**b** reacted smoothly in the presence of one equivalent of base<sup>[11]</sup> to form the intermediate carboxylates **B**, which could be combined in the same pot with Ugi 4CRs (Table 1, entries 1–3) or a Passerini  $3CR^{[3f]}$  (entry 4). The products from these 5- and 6CRs, **10a**-**c** and **11**, respectively, were isolated in 26–58% overall yield.

**Table 1:** Union of the MCR for 2*H*-2-imidazolines with the Ugi 4CR and Passerini 3CR using levulinic acid.

 $MeO \xrightarrow{O} NC + HO \xrightarrow{O} + H_2N^2R^1 \xrightarrow{MgSO_4} \frac{base (1 equiv)}{solvent, RT, 2 days}$ 4 (1 equiv) 5 (1 equiv) 6a-b (1 equiv)



Entry	R1	R <sup>2</sup> , R <sup>3</sup>	R⁴	R⁵	Yield [%]	d.r.
1	Bn	Me,Me	Су	mi (O)	26 <i>%</i> ( <b>10a</b> ) <sup>[a]</sup>	89:11 <sup>[c]</sup>
2	Bn	<i>i</i> Bu,H	tBu	in Co	49 <i>%</i> ( <b>10b</b> ) <sup>[a]</sup>	50:50 <sup>[d]</sup>
3	<i>n</i> Pr	<i>i</i> Pr,H	tBu	Bn	58% ( <b>10c</b> ) <sup>[a]</sup>	50:50 <sup>[d]</sup>
4	Bn	<i>i</i> Pr,H	tBu	-	53% (11) <sup>[b]</sup>	50:50 <sup>[d]</sup>

<sup>[</sup>a] Solvent=MeOH, base=NaOH. [b] Solvent= $CH_2Cl_2$ , base= $Et_3N$ . [c] In favor of *trans*-**10a**. [d] Only two diastereomers were observed by <sup>1</sup>H NMR spectroscopy. Cy=cyclohexyl.

Surprisingly, only two of the four possible diastereomers were observed (50:50 ratio) when aldehydes were applied in the secondary MCR (Table 1, entries 2–4). Apparently, the intermediate imidazoline carboxylates **B** epimerize at the C4 position under basic reaction conditions to give exclusively the *trans* diastereomer. Subsequent studies have shown that both the steric preference and rate of epimerization increase with steric bulk at the C5 position.<sup>[12]</sup>

Encouraged by the results obtained by incorporation of a carboxylic acid moiety at the N1 and C5 positions, we set out to introduce an additional reactive group at the C4 position by using diisocyanide  $12 a^{[13]}$  as an input in the primary MCR (Scheme 2). The two isocyanide functions in 12a have intrinsically different reactivities. The  $\alpha$ -isocyanide is  $\alpha$ -acidic and thus reacts smoothly in the 3CR to yield 2*H*-2-imidazolines. The aliphatic  $\delta$ -isocyanide remains unaffected



Scheme 2. Union of MCRs using diisocyanides 12a and 12b.

and instead provides a handle for subsequent Ugi, Passerini, and other isocyanide-based secondary MCRs.

Diisocyanide **12a** was therefore reacted with different aldehydes or ketones and amines to give intermediates **C**, which were then combined in the same pot by the Passerini 3CR to give **13a–b**, the Ugi 4CR to give **14**, or an Ugi variant<sup>[14]</sup> to give **15**. The yields for these reactions vary from good (41 %, **13a**) to excellent (**13b**, **14**, **15**, 69–78%; 95–97% per bond formation). Furthermore, **C** could be combined with a recently reported isocyanide-based MCR<sup>[15]</sup> for dihydropyrazines to give **16** in a respectable 53% yield (90% per bond formation). In the latter case, diisocyanide **12b** was used to avoid transesterification.

After the union of MCRs based on our 3CR for 2*H*-2imidazolines, we focused on combinations based on our recently reported MCR for the synthesis of *N*-(cyanomethyl)amides (Scheme 3).<sup>[10]</sup> The primary MCR between diisocyanide **17**, cyclohexanone, and morpholine in MeOH (60 °C, 5 h) yielded intermediate **D**; combination with secondary MCRs resulted in the united Ugi product **21** (BnNH<sub>2</sub>, *i*PrCHO, AcOH, room temperature, 20 h, 80%) and the Ugi–Smiles<sup>[16]</sup> product **22** (*p*-chlorobenzylamine, *n*-propanal, *o*-nitrophenol, 60 °C, 17 h, 39%). 1,2-Dichloroethane could also be used as the solvent for the first stage (80 °C, 26 h), which provided access to united Passerini product **20** 

## Communications



Scheme 3. Union of MCRs based on the MCR for N-(cyanomethyl)amides.

(*i*PrCHO, AcOH, room temperature, 22 h, 61 %) in a similar routine.

The ease and efficiency of the union of MCRs based on the 3CRs for the 2*H*-2-imidazoline and *N*-(cyanomethyl)amide scaffolds led to the design of an eight-component reaction in which both these MCRs are combined with the Ugi 4CR. Performing the MCR between 1, 2, and acetone (MeOH, room temperature, 2 days), followed by the addition of 17, 18, and 19, and heating ( $60^{\circ}$ C, 5 h) afforded intermediates A and D, respectively (Scheme 4). Neutralization of



Scheme 4. One pot 8-CR based on three sequential MCRs.

the reaction mixture (methanolic HCl) followed by the addition of benzylamine and isobutyraldehyde resulted in the formation of product **23** in 24% yield. The reaction is remarkably efficient (85% per bond formation) and constitutes, to the best of our knowledge, the first example of an 8CR.

In summary, the unique solvent and functional-group tolerance of our MCRs for the synthesis of 2*H*-2-imidazolines and *N*-(cyanomethyl)amides allow straightforward introduction of carboxylic acid and isocyanide functionalities, which can react in the same pot by Passerini and Ugi or other isocyanide-based MCRs. We have developed several new examples of 5- and 6CRs that involve up to seven new bond formations with up to nine points of diversity. Finally, we achieved a one-pot 8CR that involves nine new bond formations and eleven points of diversity. The described approach allows the construction of extremely complex and diverse druglike compounds in a single, simple operation.

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[12] The MCR between 4, 6a, and 24a–f provides imidazolines 25a–f. Analysis by <sup>1</sup>H NMR spectroscopy showed that the diastereoselectivity and/or rate of epimerization at C4 increases with larger steric differences between the R<sup>1</sup> and R<sup>2</sup> substituents. DFT geometry optimizations (B3LYP6-31G\*) support these findings. For details, see the Supporting Information.

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	$R^1 \stackrel{O}{\Vdash} R^2$	MgSO₄	$R^{1}$ $R^{2}$ $Ph$
4 (1 equiv)	24a-f (1.5 equiv)	MeOH, RT	MeO
H₂N <sup>∽</sup> Ph	<b>24a</b> : R <sup>1</sup> = H, R <sup>2</sup> = <b>24b</b> : R <sup>1</sup> = H, R <sup>2</sup> =	Me Et	О 25а–f
<b>6a</b> (1.5 equiv)	24c: R <sup>1</sup> = H, R <sup>2</sup> = 24d: R <sup>1</sup> = H, R <sup>2</sup> = 24e: R <sup>1</sup> = Me, R <sup>2</sup> 24f: R <sup>1</sup> = Me, R <sup>2</sup>	<i>i</i> Pr <i>t</i> Bu = Bn = Et	