Rapid generation of molecular complexity using "hybrid" multi-component reactions (MCRs): application to the synthesis of α-amino nitriles and 1,2-diamines†

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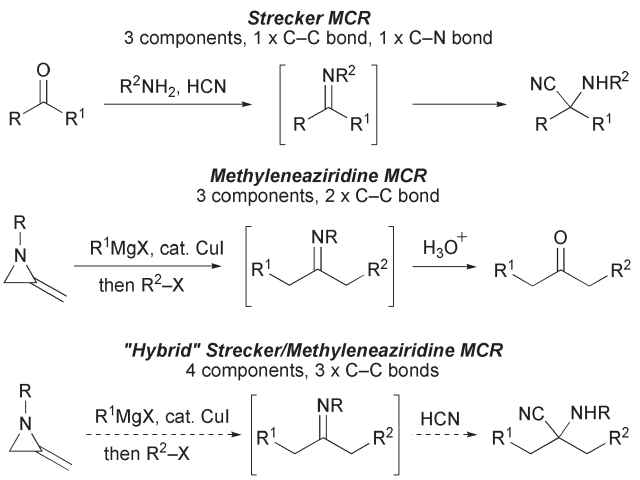
Methyleneaziridines can be converted into a wide range of 1,2-diamines and 2-cyanopiperidines in a single operation with the formation of three intermolecular carbon–carbon bonds using a "hybrid" MCR.

Multi-component reactions (MCRs) are one-pot processes in which three or more components come together to form a product containing substantial elements of all the reactants.[1,2] Well-known examples include the Strecker,[3] Passerini,[4] Ugi,[2a,5] Pauson–Khand[6] and Biginelli[7] reactions as well as the Mannich condensation.[8] MCRs provide an inherently more efficient approach to chemical synthesis than conventional bimolecular reactions, and as such efforts to develop new MCRs and related processes continue apace.[9] Of course, greater increases in molecular complexity can be achieved in an MCR when the number of reaction components is larger. Thus, four-component reactions (4-CRs) are inherently more powerful than three-component reactions (3-CRs). Unfortunately, whilst 3-CRs are quite common (*e.g.* Mannich, Strecker, Passerini, Pauson–Khand and Biginelli processes), *n*-CRs ($n \geqslant 4$) are quite rare. The enormous interest and widespread use of the Ugi 4-CR stands as strong testament to the power and utility of such "higher-order" MCRs.[2a] In this communication, we disclose a new type of 4-CR‡ that generates three new intermolecular C–C bonds by the application of a "hybrid" MCR strategy. Importantly, the approach developed could be used to transform other existing *n*-CRs into more powerful ($n + 1$)-CRs.

Analysis of existing MCRs reveals that the imine functional group plays a key role in many of them. Typically, imines are generated *in situ* by the condensation of an aldehyde (or ketone) with an appropriate amine. For example, in the Strecker 3-CR, α-amino nitrile formation proceeds *via* nucleophilic addition of HCN to the corresponding aldimine (or ketimine) (Scheme 1).[3] The adducts are readily converted into α-amino acids and related derivatives, making this reaction of considerable importance 150 years after its discovery. Recently, we reported a new 3-CR based upon methyleneaziridines,[10,11] which are readily made in two simple steps from the corresponding primary amine and 2,3-dibromopropene.[12] This 3-CR can be performed either in solution,[10] or on solid phase.[11] It involves ring opening of the highly strained aziridine ring at C-3 using a Grignard reagent under Cu(I) catalysis, and capture of the resultant metalloenamine with a carbon based electrophile (R^2–X). Simple hydrolysis of the resultant ketimine provides a one-pot method for the synthesis of 1,3-disubstituted propanones (Scheme 1). Considerable variation in the structure of all three components has been demonstrated.[10,11] Recognising that the methyleneaziridine MCR proceeds through a ketimine intermediate, we realised that by amalgamation of the Strecker and methyleneaziridine MCRs, we could produce a new "hybrid" 4-CR that could generate considerable molecular complexity in a single vessel (Scheme 1).[13]

As with any MCR, a major hurdle to be overcome is the identification of reaction conditions that are compatible with all the reagents and individual chemical steps. Thus, to achieve the addition of cyanide to ketimines after ring opening/alkylation, we needed to find a reagent system that could be used in THF, and at the same time, could be used to quench excess Grignard reagent (typically 2 eq. used) from the aziridine ring opening step. After some optimisation, we established that this could conveniently be achieved by using a combination of Me_3SiCN (1.5 eq.) and acetic acid (2.5 eq.). Under these conditions, 1-benzyl-2-methyleneaziridine (**1**) can be converted into the differentially substituted 1,2-diamines **3–10** in one-pot by way of the corresponding α-amino nitrile **2** (Scheme 2 and Table 1). In each example, *in situ* reduction with $LiAlH_4$ was undertaken because attempts to isolate the highly hindered α-amino nitriles proved difficult.[14] Full experimental procedures are provided in the Electronic Supporting Information.



Scheme 1 Rationale behind "hybrid" multi-component reaction.

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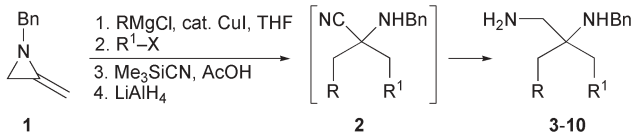


Scheme 2 Synthesis of 1,2-diamines **3–10** using MCR.

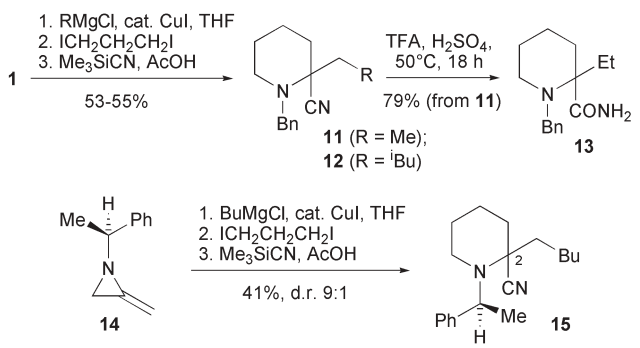
Table 1 1,2-Diamines **3–10** prepared by MCR

Entry	RMgCl	R^1–X	Diamine	% Yield[a]
1	MeMgCl	$PhCH_2Cl$	**3**	46
2	EtMgCl	$PhCH_2Cl$	**4**	41
3	BuMgCl	$CH_2{=}CHCH_2Br$	**5**	42
4	BuMgCl	$PhCH_2Cl$	**6**[b]	49
5	BuMgCl	$THPOCH_2CH_2CH_2CH_2Br$	**7**	34
6	^{i}BuMgCl	$CH_2{=}CHCH_2Br$	**8**	43
7	^{i}BuMgCl	$4\text{-}MeOC_6H_4CH_2Cl$	**9**	50
8	$PhCH_2MgCl$	$4\text{-}MeOC_6H_4CH_2Cl$	**10**	47

[a] Yield of isolated product after purification by column chromatography. [b] Structure determined by X-ray crystallography after conversion to the corresponding cyclic urea (triphosgene, Et_3N, CH_2Cl_2, 0 °C, 18 h, 69%) (see Electronic Supporting Information).[15]

In the case of diamine **6**, conversion to the corresponding cyclic urea (triphosgene, Et_3N, CH_2Cl_2, 0 °C, 18 h, 69%) provided crystals suitable for single crystal X-ray diffraction which enabled its structure, and hence that of **6**, to be unambiguously established (see Electronic Supporting Information).[15] The yields in these MCRs are quite modest (34–50%), however the efficiency with respect to each individual C–C bond forming step is good ($\geqslant$ 70%/C–C bond). Our preliminary findings suggest its tolerance with respect to changes in the structure of the methyleneaziridine, Grignard, and electrophile component are broadly in line with the simpler ketone MCR.[10,11]

Piperidines can be made by the methyleneaziridine MCR by using an electrophile bearing two leaving groups in a 1,3-relationship.[10b] Treatment of **1** with MeMgCl, 1,3-diiodopropane then HCN (generated from Me_3SiCN and AcOH) provided piperidine **11** in 55% yield by way of a 4-CR (Scheme 3). The structure of **11** was unambiguously established by X-ray crystallography of the corresponding primary amide **13** prepared by hydrolysis of the nitrile substituent (Fig. 1).[15,16] Piperidines bearing different C-2 substituents can be produced by simply changing the Grignard reagent. For example, **12** was assembled using ^{i}BuMgCl in the MCR. Although the overall yields for these conversions are again modest, efficiency is very good when viewed in the context of



Scheme 3 One-pot synthesis of 2-cyanopiperidines using MCR.

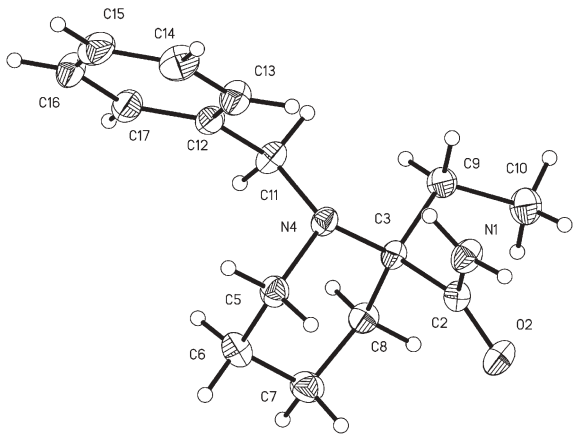


Fig. 1 ORTEP view of piperidine **13** drawn at 50% probability level.[15]

the total number of new bonds produced (3 × C–C; 1 × C–N; > 85%/bond). Encouragingly, using homochiral (*S*)-**14**, appreciable levels of asymmetric induction (d.r. 9 : 1) were observed in the formation of **15** (Scheme 3). The stereochemistry at C-2 is tentatively assigned as the (*S*)-configuration in the major diastereomer.[17]

To conclude, a "hybrid" MCR that combines the essential features of Strecker and methyleneaziridine MCRs has been developed that can be used to make a selection of α-amino nitriles and 1,2-diamines wherein three intermolecular C–C bonds are produced. In view of the prominent role of the imine functional group in other MCRs, we believe that this "hybrid" approach could be used to develop additional "higher order" *n*-CRs ($n \geqslant 4$). Work in this direction is ongoing in our laboratories.

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Notes and references

‡ This process involves the reaction of two reagents together to form an intermediate that is captured by the subsequent addition of further reagents. Hence it is more precisely defined as a sequential component reaction, see ref. 2*f*.

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13 The concept of combining two or more MCRs to increase the number of reaction components that can be brought together in a single vessel has been demonstrated previously. For a remarkable 7-CR based upon this idea, see: A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 1993, **32**, 563.

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17 This assignment is based on our earlier synthesis of (+)-coniine from (*S*)-**14** (ref. 10*b*), wherein hydride was observed to add to the *Re* face of the presumed intermediate iminium cation. Assuming cyanide attack occurs *via* the same *Re* face, the (*S*)-configuration is expected at C-2.