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Novel Multicomponent Reaction for the Combinatorial Synthesis of 2-Imidazolines

Robin S. Bon, Chongen Hong, Marinus J. Bouma, Rob F. Schmitz, Frans J. J. de Kanter, Martin Lutz,[†] Anthony L. Spek,[†] and Romano V. A. Orru*

Department of Chemistry, Vrije Universtiteit Amsterdam, De Boelelaan 1083, 1081 HV, Amsterdam, The Netherlands

orru@few.vu.nl

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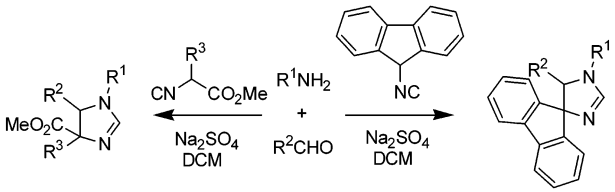
ABSTRACT



The three-component condensation between an amine, an aldehyde, and an α-acidic isocyanide efficiently provides substituted 2-imidazolines in a one-pot reaction under mild conditions.

Despite recent advances in molecular biology and the progress in combinatorial synthetic methodology, the rate of introduction of new medicines has decreased markedly over the past two decades.[1a] Structural diversity in a focused collection of potential therapeutics is believed to increase the positive hit rate. Most medicines in use are still small synthetic organic molecules that often contain a heterocyclic ring.[1a−c] However, the range of easily accessible and suitably functionalized heterocyclic building blocks for the synthesis of structurally diverse libraries is rather limited. The development of new, rapid, and clean synthetic routes toward focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists.[1] Undoubtedly, the most efficient strategies involve multicomponent reactions (MCRs), which have manifested as a powerful tool for the rapid introduction of molecular diversity.[2] Consequently, the design and development of (new) MCRs for the generation of heterocycles receives growing interest.[2a]

The 2-imidazoline scaffold is one such interesting heterocycle. Besides being widely encountered in natural products,[3] 2-imidazolines are also convenient building blocks for the synthesis of pharmaceutically relevant molecules such as azapenams, dioxocyclams, and diazapinones.[4] Imidazoline derivatives have been studied as α2-adrenoceptor or estrogen receptor modulators.[5] Their interaction with specific imidazoline binding sites results in a multiplicity of biological functions.[6] Also, suitably functionalized 2-imidazolines are easily converted to 2,3-diamino acids, which are incorporated

[†] Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH, Utrecht, The Netherlands.

(1) (a) Newton, R. *sp2* **2002**, *November*, 16−18 (see: http://www.sp2.uk.com). (b) Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 3743−3748. (c) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (d) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969.

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(3) For example, see: Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35*, 1441−1465.

(4) (a) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010−5017. (b) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586−3591.

(5) (a) Schäfer, U.; Burgdorf, C.; Engelhardt, A.; Kurz, T.; Richardt, G. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 1163−1170. (b) Rondu, F.; le Bihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, T.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J.-J. *J. Med. Chem.* **1997**, *40*, 3793−3803. (c) Gust, R.; Keilitz, R.; Schmidt, K. *J. Med. Chem.* **2001**, *44*, 1963−1970. (d) Gust, R.; Keilitz, R.; Schmidt, K.; Von Rauch, M. *J. Med Chem.* **2002**, *45*, 3356−3365.

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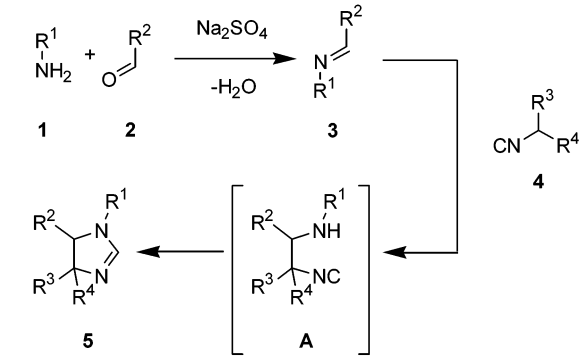
in a wide range of antibiotics and other biologically active compounds.[7] Furthermore, chiral 2-imidazolines have attracted considerable interest as templates for asymmetric synthesis[8] and as chiral ligands for asymmetric catalysis[9,10] and have found wide application as potent N-heterocyclic carbene ligands in organometallic catalysis.[10] Thus, the 2-imidazoline scaffold is considered an attractive synthetic target.

Typical synthetic procedures toward 2-imidazoline derivatives include ring closure of 1,2-diamines[11] and base-promoted aldol reaction.[12] The latter method was developed by the groups of Schöllkopf[12a] and Van Leusen[12b] simultaneously in the 1970s. Schöllkopf's procedure involves the reaction of isocyanoacetates or α-lithiated isocyanides with imines. Van Leusen used TosMIC and its derivatives as α-acidic isocyanides to synthesize imidazoles[13] via 4-tosyl-2-imidazolines. Recently, imidazoline chemistry regained attention and some catalytic diastereo- and enantioselective routes toward 2-imidazolines have been reported.[14] However, most syntheses were performed in a stepwise fashion and were not set up as MCR.[15] They are therefore not suited for the combinatorial synthesis of small focused libraries of 2-imidazolines. Our main objective was the translation of the aldol synthesis of 2-imidazolines to an elegant and flexible MCR and to determine its scope with respect to the input components. In this communication, preliminary results are presented.

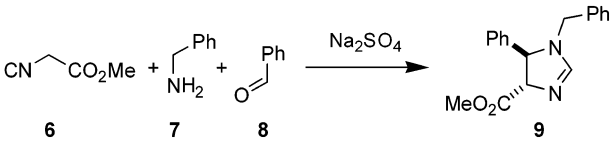
We envisioned a MCR toward 2-imidazolines of type **5** to proceed through in situ formation of imines **3** from amines **1** and aldehydes **2**, followed by attack of the α-acidic isocyanide **4** and subsequent ring closure (Scheme 1). Traces of amine present in the reaction mixture may act as a basic catalyst to promote α-addition to generate the tentative intermediate **A**.[12a]

Scheme 1



From previous work in this area, it seemed reasonable to use isocyanoacetate **6**. However, the initial results for the MCR combining **6** with benzylamine **7** and benzaldehyde **8** were disappointing (Table 1). Even after prolonged stirring

Table 1. Initial MCR for the Synthesis of 2-Imidazolines Using **6**



entry	conditions	scale (mmol)	yield[a] (%)
1	MeOH, rt, 3 days	1	<5[b]
2	MeOH, rt, 18 h	5	34[b]
3	DCM, rt, 3 days	1	0

[a] Isolated yields. [b] Only the anti diastereomer (^{1}H NMR) of **9** was found.

in MeOH, only traces of 2-imidazoline **9** were formed (entry 1). Also, in our hands, reaction times between **6** and the preformed imine of **7** and **8** proved to be significantly longer than those reported earlier.[16] However, when the reaction was performed at a larger scale (entry 2), a reasonable amount of **9** could be isolated. On the other hand, stirring the same components in DCM gave no detectable 2-imidazoline **9**.

Interesting in this respect is that isocyanoacetate **6** can be easily applied in Ugi four-component condensations (Ugi-4CC).[17] A reaction between **6**, isopropylamine **10**, isobutyraldehyde **11**, and propionic acid **12** provides the bisamide **13** in 81% yield (Scheme 2).

2-Phenylisocyanoacetate **16** has a more acidic α-H compared to **6** and should serve as a more appropriate isocyanide

(6) Gentili, F.; Bousquet, P.; Brasili, L.; Dontenwill, M.; Feldman, J.; Ghelfi, F.; Gianella, M.; Piergentili, A.; Quaglia, W.; Pigini, M. *J. Med. Chem.* **2003**, *46*, 2169−2176.

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(8) (a) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707−1710. (b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1711−1714. (c) Dalko, P. I.; Langlois, Y. *Chem. Commun.* **1998**, 331−332.

(9) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713−4716.

(10) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309 and references therein.

(11) (a) Riebsomer, J. L. *J. Am. Chem. Soc.* **1948**, *70*, 1629−1631. (b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707−1710.

(12) (a) Meyer, R.; Schöllkopf, U.; Böhme, P. *Liebigs Ann. Chem.* **1977**, 1183−1193. (b) van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153−1159.

(13) Recently, a multicomponent synthesis of imidazoles using van Leusen's TosMIC chemistry was published: Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516−1524.

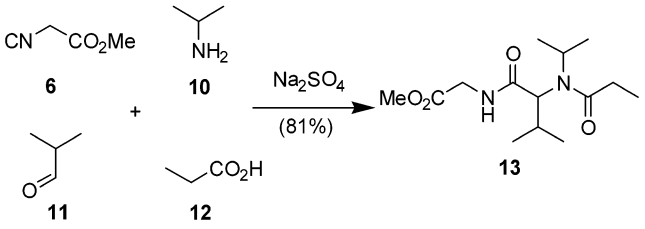
(14) (a) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969−4972. (b) Lin, Y.-R.; Zhou, X.-T.; Dai, L.-X.; Sun, J. *J. Org. Chem.* **1997**, *62*, 1799−1803. (c) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331−1334.

(15) Notable exception is the highly diastereoselective multicomponent synthesis of imidazolines employing oxazolones in 1,3-dipolar cycloaddition reactions reported by: Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, *4*, 3533−3535.

(16) Schöllkopf reported that reactions between the isocyanoacetate **6** and imines at 10 mmol scale in methanol were usually complete after 3 h. See also ref 12a.

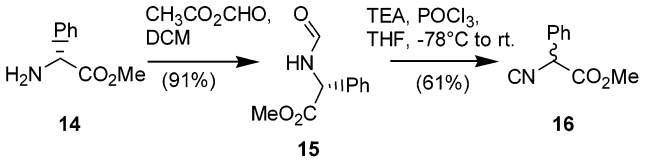
(17) (a) Lehnhoff, S.; Goebel, M.; Karl, R. M.; Klösel, R.; Ugi, I. *Angew. Chem.* **1995**, *107*, 1208−1211. (b) Cheng, J.-F.; Chen, M.; Arrhenius, T.; Nadzan, A. *Tetrahedron Lett.* **2002**, *43*, 6293−6296. (c) Bradley, H.; Fitzpatrick, G.; Glass, W. K.; Kunz, H.; Murphy, P. V. *Org. Lett.* **2001**, *3*, 2629−2632.

Scheme 2



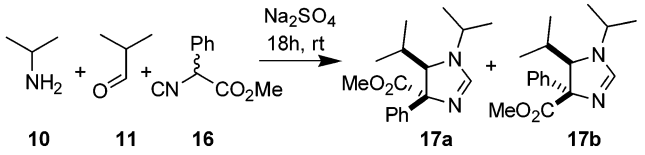
component in the MCR of Scheme 1. Racemic **16** was synthesized from *D*-phenylglycine methyl ester **14** via the *N*-formamide **15** in 55% yield (Scheme 3).[18]

Scheme 3



The MCR using **16** together with **10** and **11** afforded the desired 2-imidazolines **17** in reasonable yields depending on the solvent used (Table 2). In MeOH, DCM, and toluene,

Table 2. MCR for the Synthesis of 2-Imidazolines Employing **16**



entry	solvent	yield[a] (%)	ratio of **17a**:**17b**[b,c]
1	MeOH	67	75:25
2	DCM	74	75:25
3	toluene	62	75:25
4	THF	10	75:25

[a] Isolated yields. [b] Diastereomeric ratios were calculated from ^{1}H NMR spectra. [c] Relative stereochemistry of **17a** was determined using X-ray diffraction.

comparable yields were obtained (entries 1−3), whereas in THF, almost no formation of **17** was observed (entry 4). It is important to note that the use of carboxylic acid **12**, together with **10**, **11**, and **16**, in a procedure similar to that described above for **6** (Scheme 2) only gave **17**. The expected Ugi-4CC product was not formed. Apparently, the carboxylic acid does not participate in this MCR.

Formation of the anti diastereomer **17a** is favored over formation of the syn diastereomer **17b** and is independent of the solvent used (Table 2). X-ray data of **17a** unambiguously proved the anti relationship between the methyl ester at C(4) and isopropyl substituent at C(5) (Figure 1).[19a]

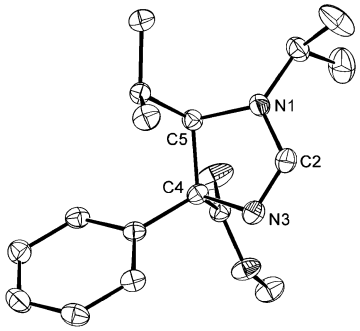


Figure 1. Displacement ellipsoid plot of **17a**. Drawn at the 50% probability level. H-atoms are omitted for clarity.

The scope of this MCR was further elaborated. One-pot combination of **16** with functionalized aliphatic, aromatic, or benzylic amines and aliphatic, (hetero)aromatic, or α,β-unsaturated aldehydes provides a range of imidazolines (Figure 2; **18**−**26**). Except for the reaction with sterically demanding benzhydrylamine (formation of **18**),[20] all reactions went smoothly and the products were obtained in fair to good yields (47−91%).[21]

In analogy with **17a**, whose relative configuration was confirmed by X-ray crystal structure determination (vide supra), ^{1}H NMR data were used to assign the relative configuration at C(4) and C(5) of **18**−**26**.[19] Without exception, the anti products were formed predominantly. Interestingly, Spartan semiempirical PM3 calculations show that, in general, the syn diastereomers are energetically favored over the anti isomers. However, the calculations suggest that formation of the anti diastereomers proceeds via favored intermediates **A** and is easier than formation of the syn diastereomers.

Besides isocyanoacetates, other isocyanides with acidic α-protons, e.g., 9-isocyanofluorene **29** (becomes aromatic upon deprotonation), react in a similar fashion with in situ-

(18) (a) Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079−4082. (b) Isocyanoacetate **16** turned out to be somewhat unstable toward silica column chromatography and possesses an unpleasant odor. Other reagents for the dehydration of *N*-formamide **15** were tested, like Burgess' reagent, TsCl/pyridine, and triphosgene/NMM. Unfortunately, no optically active isocyanide could be obtained.

(19) (a) For X-ray details, including the CIF file, see Supporting Information. (b) Analysis of all ^{1}H NMR spectra revealed for H(5) a characteristic $\Delta\delta$(anti−syn) = 0.6 ± 0.05. The upfield shift of H(5) in the spectra of the syn diastereomers can be explained by a shielding effect of the Ph-group at C(4). This is confirmed by NOE measurements.

(20) Considerable amounts of imine are isolated in this case, and **16** presumably decomposes before the reaction is complete. That 2-imidazoline formation with sterically demanding amines proceeds relatively slow is supported by the observation that combination of benzhydrylamine, **11**, **12**, and **16** only gave (within 18 h) the corresponding Ugi-4CC product in 60% yield.

(21) Reactions all proceed at room temperature and only require the addition of Na_2SO_4 to remove water, which is formed during initial imine formation. See Supporting Information for details.

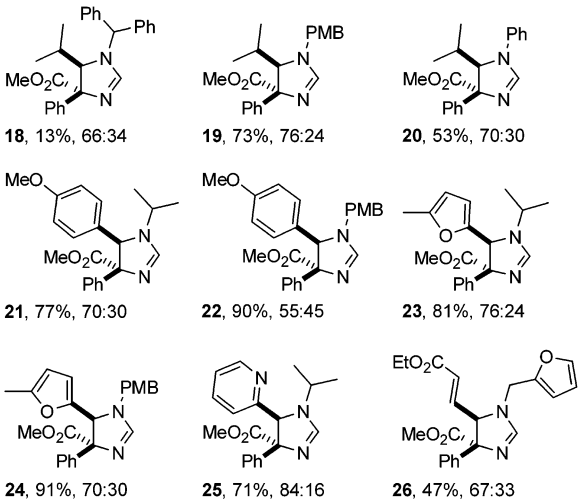
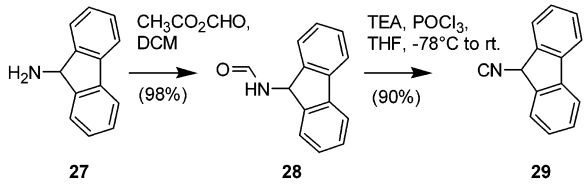


Figure 2. Series of 2-imidazolines synthesized from **16**. Ratios refer to anti:syn; only the major diastereomer is depicted.

generated imines. The stable, crystalline, almost odorless **29** can be prepared from **27** in 88% using the procedure described for **16** (Scheme 4).

Scheme 4



Condensation of **29** with a variety of functionalized amines (aliphatic, benzylic, or furfuryl) and aldehydes (aliphatic, (hetero)aromatic, or α,β-unsaturated) provides spiro-2-imidazolines **30**−**39** (Figure 3). The yields were generally good (up to 91%), but once more, application of benzhydrylamine resulted in an unsatisfying yield (**30**, 20%).[22] Steric constraints in the amine component seem to determine the limitations of this MCR.

In summary, the stepwise aldol synthesis of 2-imidazolines was successfully translated to a flexible MCR suited for

(22) When **29** is combined with **10**, **11**, and propionic acid **12**, the same trend as for **16** can be recognized. Formation of 2-imidazoline **31** was exclusive (70%) and no Ugi-4CC product was observed. However, a similar reaction, but now with benzhydrylamine instead of isopropylamine (**10**) as amine input, gave no 2-imidazoline. The bisamide, resulting from an Ugi-4CC, was isolated as the only reaction product in 67%.

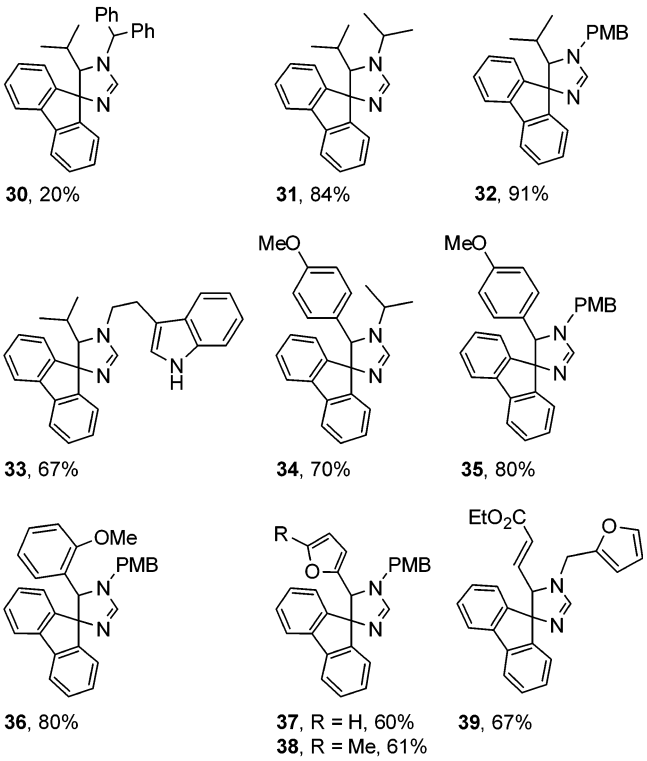


Figure 3. Series of spiro-2-imidazolines synthesized from **29**.

combinatorial application. Both 2-phenylisocyanoacetate **16** and 9-isocyanofluorene **29** were shown to be appropriate isocyanide components in this reaction. The results indicate that the MCR is compatible with a large range of amine and aldehyde components. However, the use of sterically demanding amines results in lower yields. Currently, other isocyanides with acidic α-protons are under investigation. Further, we are exploring one-pot methods to prepare highly complex polycyclic structures using the MCR described here.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and X-ray crystallographic details of **17a** (CIF file; atomic coordinates, displacement parameters, bond lengths and angles, and torsion angles). This material is available free of charge via the Internet at http://pubs.acs.org.

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