

# Diastereoselective Multicomponent Synthesis of Dihydropyridones with an Isocyanide Functionality

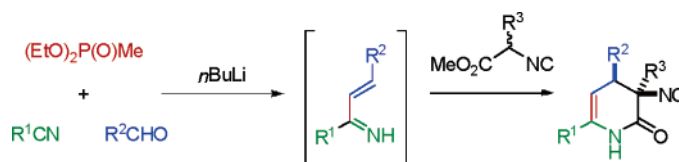
Monica Paravidino, Robin S. Bon, Rachel Scheffelaar, Danielle J. Vugts, Anass Znabet, Rob F. Schmitz, Frans J. J. de Kanter, Martin Lutz,<sup>†</sup> Anthony L. Spek,<sup>†</sup> Marinus B. Groen, and Romano V. A. Orru\*

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

orru@few.vu.nl

Received September 6, 2006

## ABSTRACT



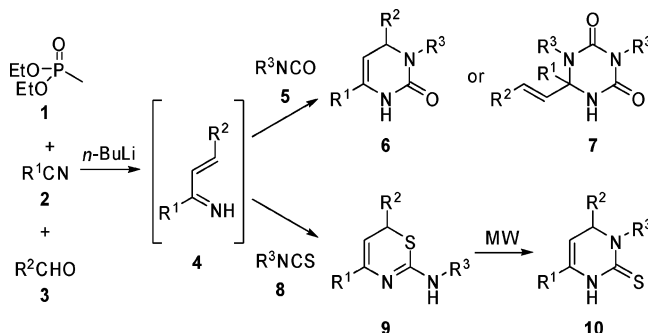
In a search for new multicomponent strategies leading to valuable small heterocycles, a new highly diastereoselective four-component reaction (4CR) was found in which a phosphonate, nitriles, aldehydes, and isocyanacetates combine to afford functionalized 3-isocyano-3,4-dihydro-2-pyridones. In this strategy, initially a 1-azadiene is generated, which is trapped in the same pot by an isocyanacetate as the fourth component. Multicomponent reactions (MCRs) that lead to heterocycles containing isocyano substituents are unprecedented and offer many possibilities for further differentiation.

Multicomponent reactions (MCRs) receive significant attention in synthetic method development<sup>1</sup> because they are well-suited for the easy construction of diversified arrays of, e.g., valuable heterocyclic scaffolds.<sup>2</sup> Methods that employ a common reactive intermediate in a modular synthetic sequence are particularly appreciated because these allow the quick generation of scaffold diversity. We contributed to this area recently with a novel MCR that combines in situ generated 1-azadienes **4** with electron-poor isocyanates **5** to afford functionalized 3,4-dihydropyrimidine-2-ones **6** (Scheme 1).<sup>3a</sup> Reaction of **4** with other cyclization partners gives

access to triazinanediones **7**,<sup>3a</sup> 2-aminothiazines **9**,<sup>3b</sup> and dihydropyrimidine-2-thiones **10**.<sup>4</sup>

To further explore the potential of this procedure, we examined the four-component reaction (4CR) among diethyl methylphosphonate **1**, benzonitrile **11**, *p*-methoxybenzal-

Scheme 1. 1-Azadienes **4** in Modular Synthetic Sequences



<sup>†</sup> Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands.

(1) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (b) Zhu, J. P. *Eur. J. Org. Chem.* **2003**, *7*, 1133–1144.

(2) (a) Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471–1499. (b) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1–140.

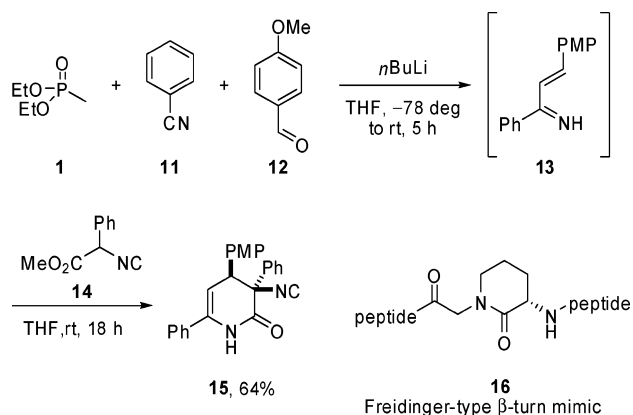
(3) (a) Vugts, D. J.; Jansen, H.; Schmitz, R. F.; De Kanter, F. J. J.; Orru, R. V. A. *Chem. Commun.* **2003**, 2594–2595. (b) Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F.; De Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem.–Eur. J.* **2006**, *12*, 7178–7189.

**Table 1.** One-Pot Reaction among **1**, **11**, **14**, and Various Aldehydes<sup>d</sup>

Entry	Aldehyde	Product	Yield <sup>[a]</sup>	Entry	Aldehyde	Product	Yield <sup>[a]</sup>
1			72% <sup>[b]</sup>	5			0%
2			98% <sup>[b]</sup>	6			0%
3			0%	7			64% <sup>[b]</sup>
4			36% <sup>[b]</sup>	8			77% <sup>[b,c]</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> Only the 3,4-cis-diastereomer was detected in the <sup>1</sup>H NMR of the crude product. <sup>c</sup> A 1:1 mixture of diastereomers was isolated. <sup>d</sup> PCP = *p*-chlorophenyl; PNP = *p*-nitrophenyl.

hyde **12**, and methyl 2-isocyano-2-phenylacetate **14** (Scheme 2). The product, 3,4-dihydropyridin-2-one (3,4-DHP-2-one)

**Scheme 2.** Synthesis of 3,4-DHP-2-one **15**

**15**, was isolated as a single diastereomer in good yield. In contrast to other MCRs employing  $\alpha$ -acidic isonitriles **14**,<sup>5</sup> the isocyano group is not incorporated in the ring but stays intact. To the best of our knowledge, no MCRs have been reported that lead to heterocycles containing isocyano substituents. In this way, synthetically very useful complex

isocyanides become easily available. For example, DHP-2-ones such as **15** have great potential in the construction of Freidinger-type  $\beta$ -turn mimics (**16**).<sup>6</sup> They contain a rigid framework with a double bond suitable for further functionalization. The isocyano group is an excellent synthetic handle for additional MCRs, and the free amido nitrogen is a versatile anchor for derivatization. 3,4-DHP-2-ones are conformationally similar to dihydropyridines and as such have great potential as calcium channel modulators.<sup>7,8</sup> Furthermore, they have been used extensively in the synthesis of complex natural products.<sup>9</sup>

Numerous routes to 3,4-DHP-2-ones are known. Many involve an aza-annulation of enamines and carboxylic acid

(4) Glasnov, T. N.; Vugts, D. J.; Koningstein, M. M.; Desai, B.; Fabian, W. M. F.; Orru, R. V. A.; Kappe, C. O. *QSAR Comb. Sci.* **2006**, *25*, 509–518.

(5) (a) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; De Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Lett.* **2003**, *5*, 3759–3762. (b) Bon, R. S.; Van Vliet, B.; Sprengels, N. E.; Schmitz, R. F.; De Kanter, F. J. J.; Stevens, C. V.; Swart, M.; Bickelhaupt, F. M.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2005**, *70*, 3542–3553.

(6) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooke, J. R.; Saperstein, R. *Science* **1980**, *210*, 656–658.

(7) Ochoa, E.; Suarez, M.; Verdecia, Y.; Pita, B.; Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Duque, J.; Pomes, R. *Tetrahedron* **1998**, *54*, 12409–12420.

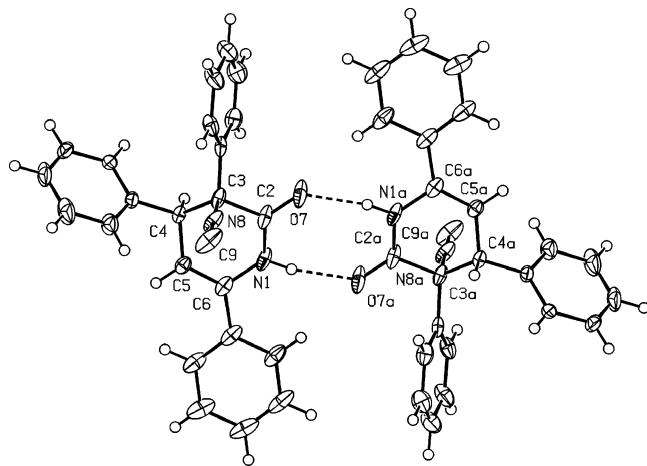
(8) Rodríguez, H.; Suarez, M.; Pérez, R.; Petit, A.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 3709–3712.

(9) Stille, J. R.; Barta, N. S. *Studies in Natural Products Chemistry*; Elsevier Science: Amsterdam, 1996; Vol. 18, pp 315–389.

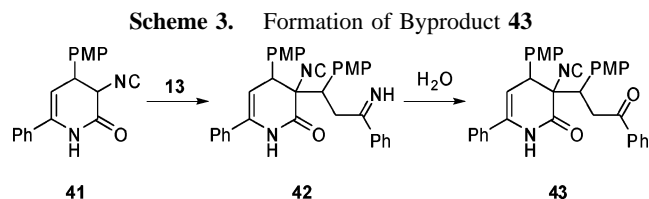
derivatives or nitriles.<sup>8–10</sup> Also, reactions between 1-azadienes and oxazolones,<sup>11</sup> ketenes,<sup>12</sup> or  $\alpha$ -metallated acetate derivatives<sup>13</sup> are reported. However, the possibilities for differentiation displayed by **15** are unprecedented and therefore we decided to investigate the scope of this novel MCR.

The one-pot combination of various aldehydes with **1**, **11**, and **14** is depicted in Table 1. The choice of aldehyde is crucial. Aromatic and heteroaromatic aldehydes give the expected DHP-2-ones in reasonable to excellent yield (entries 1, 2, and 4 and Scheme 2). Strongly electron-deficient *p*-nitrobenzaldehyde **21** represents an exception and leads to a complex mixture of products (entry 3). Application of the aliphatic aldehyde **25** results in aldol condensation products (entry 5), but blocking the  $\alpha$ -position of the aldehyde did not give better results (**27**, entry 6). However,  $\alpha,\beta$ -unsaturated aldehydes are suitable inputs as was demonstrated using **29** and (1*R*)-(–)-myrtenal **31** (entries 7 and 8). In all cases, only the 3,4-*cis*-isomers were formed. Use of the optically pure **31** did not show any chiral induction, so **32** was isolated as a 1:1 mixture of diastereomers.

The X-ray crystal structure of **20** unambiguously confirms the *cis* relationship between the isocyano group at C-3 and the phenyl group at C-4 (Figure 1). In addition, the



the standard reaction conditions, the expected 3,4-DHP-2-one **41** in only 19% yield (trans/cis = 67:33) together with **43** (18%). The initially formed **41** probably undergoes a fast reaction with azadiene **13** which is still present in the reaction mixture (Scheme 3). Hydrolysis of the resulting imine **42**



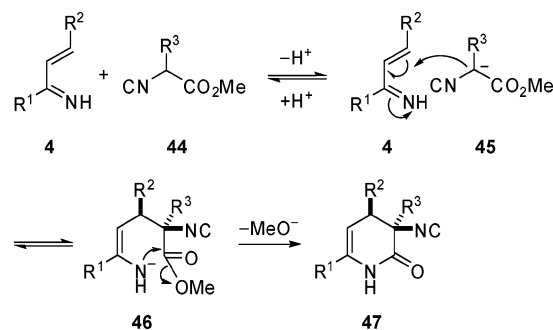
during workup/purification affords ketone **43**. Formation of **43** was completely prevented using a reverse addition strategy, and **41** could be obtained in 32% yield (Table 2, entry 5). This shows that isocyanoacetates lacking additional electron-withdrawing  $\alpha$ -substituents are sufficiently reactive in our MCR, which further broadens the scope. To further improve the reactivity and increase the yields of this type of 3,4-DHP-2-ones, Ag(I) catalysis can be considered.<sup>5b,15</sup>

The isolation of product **43** suggests that the formation of **47** proceeds via Michael-type attack of the anion **45** to **4** and subsequent lactamization of the intermediate **46** (Scheme 4). Spartan semiempirical PM3 calculations ( $R^1 = R^2 = R^3 = \text{Ph}$ ) indicate that in the reaction between **45** and **4** formation of *cis*-**46** is favored.

In conclusion, a program set up to generate scaffold diversity using modular synthetic sequences led to a novel,

(15) Grigg, R.; Lansdell, M. I.; Thornton-Pett, M. *Tetrahedron* **1999**, *55*, 2025–2044.

**Scheme 4.** Possible Mechanism of the Cycloaddition



highly diastereoselective, and versatile MCR for 3,4-DHP-2-ones. Currently, further variation of the  $R^3$  group is under investigation. Furthermore, the unprecedented 3-isocyano-3,4-DHP-2-ones are being used in Passerini and Ugi reactions, leading to new six- or seven-component reactions. The products will be developed toward potential  $\beta$ -turn mimics.

**Acknowledgment.** We thank Dr. Marek Smoluch (Vrije Universiteit Amsterdam) for conducting (HR)MS measurements. This work was financially supported by the Dutch science foundation (NWO-VICI and NWO-JC).

**Supporting Information Available:** Experimental procedures and characterizations including a cif file. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL062204B