DOI: 10.1002/ejoc.201101567

Exploiting the Divergent Reactivity of Isocyanoacetates: One-Pot Three-Component Synthesis of Functionalized Angular Furoquinolines

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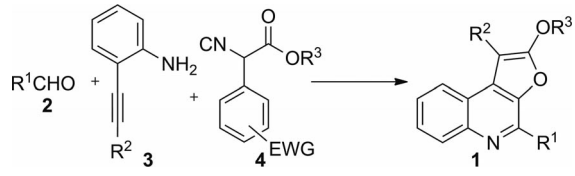
Keywords: Fused-ring systems / Nitrogen heterocycles / Multicomponent reactions / Cycloaddition

A one-pot, three-component synthesis of polysubstituted furo[2,3-*c*]quinoline **1** was developed based on the new reactivity profile of α-(4-nitrophenyl)-α-isocyanoacetates. Simply mixing aldehydes **2**, *ortho*-alkynylanilines **3**, and α-(4-nitrophenyl)-α-isocyanoacetates **4** in methanol at room temperature, followed by addition of toluene and heating to reflux, provided the polysubstituted furo[2,3-*c*]quinolines in moderate to excellent yields. Mechanistically, the three-component reaction of **2**, **3**, and **4** leading to 5-alkoxyoxazoles was followed by a domino sequence involving Diels–Alder/retro-Diels–Alder/oxidation reactions. In this one-pot process, five chemical bonds were created with concurrent formation of two heterocyclic rings. The reaction was performed under thermal conditions and no external reagent was needed to promote this mechanistically intriguing reaction.

Introduction

Quinolines and hetero-fused quinolines are ubiquitous structural motifs found in a large number of biologically important alkaloids, and they are considered privileged scaffolds in medicinal chemistry. Furoquinolines are one of the most important members of this class of heterocycles.[1,2] They are constituents of the *Rutaceae* and *Solanaceae* plant species[3] and possess a wide range of biological properties including antimicrobial, antitumor, antiemetic, antineoplastic, and antimalarial activities.[2a,4] Therefore, they are important targets for organic synthesis and much effort has been directed towards the development of the efficient construction of furoquinolines. Most of the classical synthetic approaches use a stepwise "ring-by-ring" process that is often low yielding and do not allow the introduction of molecular diversity.[3,5,6] While more efficient synthetic routes have recently been developed for linear furoquinolines,[7] progress still remains to be made in the synthesis of angular furoquinolines.[8] A few years ago, we disclosed a one-pot synthesis of 2-*N*,*N*-dialkylaminofuro[2,3-*c*]-quinolines through a multicomponent domino reaction[9,10] of *ortho*-alkynylanilines, α-isocyanoacetamides, and aldehydes.[11] Herein, we report a highly efficient multicomponent synthesis of 2-alkoxyfuro[2,3-*c*]quinolines **1** by using α-(4-nitrophenyl)-α-isocyanoacetates as a key reaction partner (Scheme 1).



Scheme 1. Synthesis of 2-alkoxyfuro[2,3-*c*]quinolones **1**.

On the basis of the substrate design approach,[12] we have been able to fine-tune the reactivity of α-isocyanoacetates by simply introducing an additional electron-withdrawing group in its α-position. We demonstrated that α-(*p*-nitrophenyl)-α-isocyanoacetates[13] display a reactivity profile similar to that of α-isocyanoacetamides,[11,14,15] rather than that of the parent α-isocyanoacetates, which is dominated by the nucleophilicity of the α-carbanion.[16] We have subsequently developed multicomponent syntheses of 5-alkoxyoxazoles, furopyrrolones, and pyrrolopyridinones by taking advantage of the peculiar reactivity of this type of α-isocyanoacetate.[13]

Taking advantage of the potential chemical reactivity of 5-alkoxyoxazoles, a three-component synthesis of 2-alkyloxyfuroquinolines **1** from aldehydes **2**, *ortho*-alkynylanilines **3**, and α-isocyanoacetates **4** was envisaged according to the sequence shown in Scheme 2. Thus, condensation of aldehydes **2** and amines **3** should give imines **5**, which would react with the divalent isocyanide carbon atom of α-isocyanoacetates **4** to produce 5-alkoxyoxazoles **7**. Intramolecular Diels–Alder cycloaddition[17] of **7** between the oxazole and the tethered triple bond would furnish oxa-bridged heterocycles **8**, which could undergo fragmentation by a retro-

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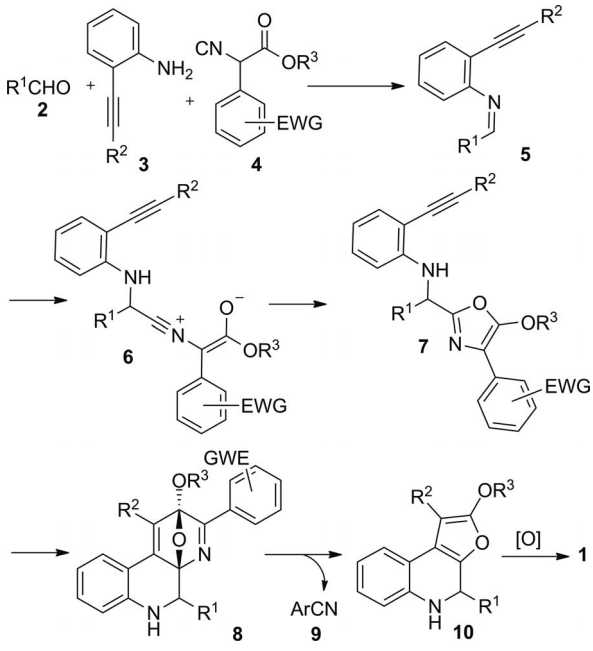
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101567.

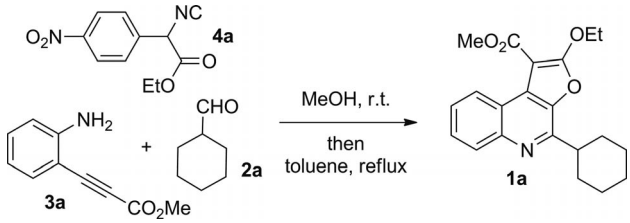
Diels–Alder process to furnish **10** and benzonitrile derivatives **9**. A subsequent oxidation mediated by atmospheric oxygen could occur to give aromatic 2-alkoxyfuro[2,3-*c*]-quinolines **1**. In this complex domino transformation, we assumed that the two irreversible steps, formation of the oxazole and the retro-Diels–Alder reaction, would provide the driving forces to guarantee the success of the overall multicomponent domino process.



Scheme 2. Three-component domino process to furoquinolines, a mechanistic working hypothesis.

Results and Discussion

To validate our hypothesis, cyclohexanecarbaldehyde (**2a**), methyl 3-(2-aminophenyl)propiolate (**3a**) and ethyl α-(*p*-nitrophenyl)-α-isocyanoacetate (**4a**) were selected as test substrates to survey the reaction conditions. When the reaction was carried out in toluene (c = 0.1 M) at room temperature or at reflux, neither 2-alkoxyfuro[2,3-*c*]quinoline **1a** nor 5-alkyloxyoxazole **7** was formed (Scheme 2). Addition of promoters (1.0 equiv.) such as NH_4Cl, I_2, LiBr, $ZnCl_2$, Et_3N, *p*TSA, or camphorsulfonic acid failed to trigger the reaction efficiently. The undesired ring–chain tautomerization of isocyanoacetate **4a** leading to the 2-unsubstituted oxazole was instead observed under these conditions.[18] In polar solvents, such as methanol, only a trace amount of oxazole was detected.[19] However, increasing the concentration of the reaction mixture had a dramatic effect, and when the reaction was performed in methanol at 1.0 M, the three-component reaction went to completion at room temperature leading to oxazole **7** after 22 h. Performing the reaction at higher temperature under otherwise identical conditions did not give the desired Diels–Alder product. Fortunately, addition of toluene to the reaction mixture followed by heating to reflux for 5 h afforded 2-alkoxyfuro[2,3-*c*]-quinoline **1a** in 89% yield (Scheme 3). 4-Nitrophenylcyanide (**9a**), formed during the retro-Diels–Alder step, was also isolated from the reaction mixture. It is interesting to note that at least six distinct elementary reactions, including condensation of an aldehyde with an amine, nucleophilic addition of an isocyanide to an imine, oxazole formation, intramolecular Diels–Alder cycloaddition of the oxazole, retro-Diels–Alder, and oxidation, occurred in an ordered manner to provide α-alkoxyfuro[2,3-*c*]quinolines **1**. It is worth to note that two rings were created with concurrent formation of five chemical bonds. The efficiency of this three-component reaction (89% yield) is therefore remarkably high if one counts the yield per chemical bond formation.



Scheme 3. Survey of reaction conditions for the three-component domino synthesis of α-alkoxyfuro[2,3-*c*]quinoline **1a**.

The scope of this novel domino multicomponent reaction was next examined by varying the structure of the amines and aldehydes (Figure 1). Because the 4-nitrophenyl substituent of isocyanide **4a** is not incorporated into the structure of the final product, the invariableness of this input is not a major concern in this reaction. By applying the standard conditions (MeOH, r.t.; then toluene, reflux), the furoquinolines were isolated in moderate to excellent yields from both aliphatic and aromatic aldehydes having different electronic and steric properties (Figure 2). When aniline derivatives **3c** (R = NO_2) and **3d** (R = COMe)[20] bearing electron-poor acetylene units were subjected to the same conditions, the reaction slowed down significantly. Fortunately, desired 2-alkoxyfuroquinolines **1h** and **1i** (Figure 2) were isolated in

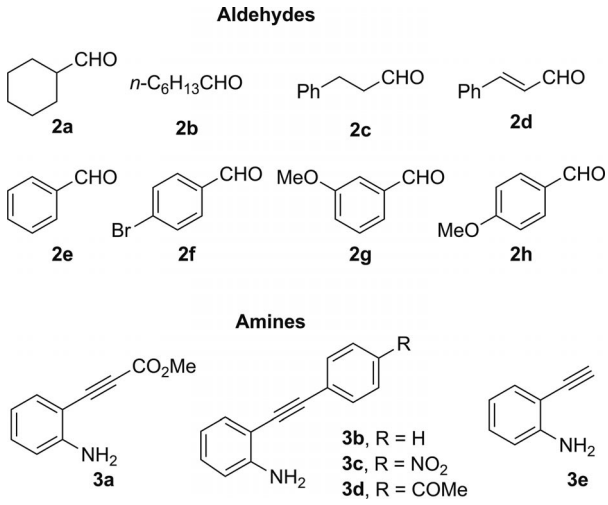


Figure 1. Structures of amines and aldehydes.

excellent yields when the reaction was performed in refluxing xylene instead of toluene. Gratefully, aniline **3b** (R = H) bearing an electronically neutral acetylene unit and aniline **3e** bearing a terminal acetylene unit participated in the reaction efficiently to afford the corresponding adducts **1k** and **1j** in 78 and 58% yield, respectively.

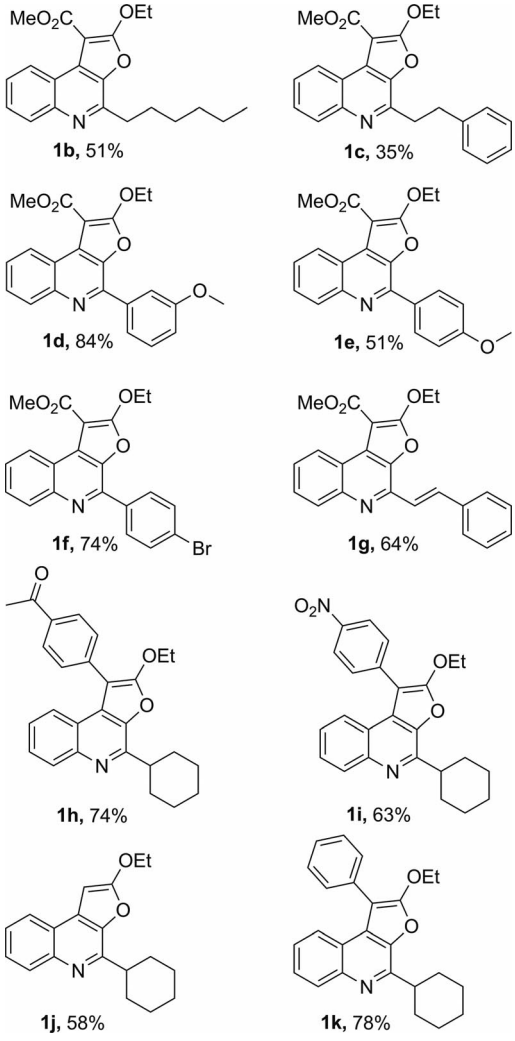


Figure 2. Furo[2,3-*c*]quinolines synthesized.

Conclusions

In summary, we described a three-component synthesis of functionalized 2-alkoxyfuroquinolines from readily available starting materials. A novel reactivity of α-isocyanoacetates bearing electron-withdrawing substituents at the α-position and the diene properties of the 5-alkoxyoxazoles were exploited to orchestrate the reaction sequence. It is interesting to note that no external reagent was required and heating was the only external force needed to promote this mechanistically complex reaction that led to the creation of five chemical bonds and two heterocyclic rings. The operational simplicity and good chemical yields make this novel heterocycle synthesis appealing in diversity-oriented synthesis.[21]

Experimental Section

Representative Procedure for the Three-Component Synthesis of α-Alkoxyfuro[2,3-*c*]quinolones 1: Aldehyde **2a** (1.0 mmol) and amine **3a** (1.0 mmol) were dissolved in methanol (1.0 mL) and stirred for 30 min. α-Isocyanoacetate **4a** (1.0 equiv.) was added and stirring was continued at room temperature until the disappearance of the α-isocyanoacetate. Toluene (1 mL) was added, and the reaction was heated at reflux for 5 h. The crude product was purified by flash column chromatography on silica gel (heptanes/EtOAc, 3:1) to give desired furoquinoline **1a** (89%) as a white solid. M.p. 96–97 °C. IR: $\tilde{\nu}$ = 2933, 2850, 1702, 1575, 1452, 1359, 1256, 1086, 1013, 872, 760 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.26 (dd, J = 8.4, 1.2 Hz, 1 H), 8.12 (dd, J = 8.4, 1.2 Hz, 1 H), 7.66 (ddd, J = 8.4, 6.9, 1.2 Hz, 1 H), 7.55 (ddd, J = 8.4, 6.9, 1.2 Hz, 1 H), 4.74 (q, J = 7.1 Hz, 2 H), 3.99 (s, 3 H), 3.27 (m, 1 H), 1.80–2.09 (m, 7 H), 1.63 (t, J = 7.1 Hz, 3 H), 1.38–1.60 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 164.8 (Cq), 163.9 (Cq), 151.1 (Cq), 145.5 (Cq), 139.5 (Cq), 129.2 (CH), 129.0 (Cq), 127.7 (CH), 126.5 (CH), 125.3 (CH), 122.3 (Cq), 90.0 (Cq), 68.4 (CH_2), 51.5 (CH_3), 42.9 (CH), 31.0 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 14.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_{21}H_{24}NO_4$ $[M + H]^+$ 354.1705; found 354.1707.

Supporting Information (see footnote on the first page of this article): Full characterization data and copies of the ^1H and ^{13}C NMR spectra.

Acknowledgments

Financial support from the Centre National de la Recherche Scientifique (CNRS) is gratefully acknowledged. M. B. thanks the Institut de Chimie des Substances Naturelles (ICSN) for a doctoral fellowship.

[1] a) M. Balasubramanian, J. G. Keay in *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Elsevier, **1996**, vol. 5, pp. 245–300; b) J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 650–668; c) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627–646; d) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 223–246.

[2] a) O. Schimmer, I. Kuhne, *Mutat. Res.* **1991**, *249*, 105; b) L. W. Deady, A. J. Kaye, G. J. Finlay, B. C. Baguley, W. A. Denny, *J. Med. Chem.* **1997**, *40*, 2040–2046; c) O. Billker, V. Lindo, M. Panico, A. E. Etienne, T. Paxton, A. Dell, M. Rogers, R. E. Sinden, H. R. Morris, *Nature* **1998**, *392*, 289–292; d) J. M. Fortune, L. Velea, D. E. Graves, T. Utsugi, Y. Yamada, N. Osheroff, *Biochemistry* **1999**, *38*, 15580–15586; e) P. Camps, R. El Achab, J. Morral, D. Munoz-Torrero, A. Badia, J. E. Banos, N. M. Vivas, X. Barril, M. Orozco, F. J. Luque, *J. Med. Chem.* **2000**, *43*, 4657–4666; f) G. Roma, M. Di Braccio, G. Grossi, F. Mattioli, M. Ghia, *Eur. J. Med. Chem.* **2000**, *35*, 1021–1035; g) P. Camps, E. Gomez, D. Munoz-Torrero, A. Badia, N. M. Vivas, X. Barril, M. Orozco, F. J. Luque, *J. Med. Chem.* **2001**, *44*, 4733–4736; h) P. M. S. Chauhan, S. K. Srivastava, *Curr. Med. Chem.* **2001**, *8*, 1535–1542; i) Y.-L. Chen, K.-C. Fang, J.-Y. Sheu, S.-L. Hsu, C.-C. Tzeng, *J. Med. Chem.* **2001**, *44*, 2374–2377; j) A. R. Martirosyan, R. Rahim-Bata, A. B. Freeman, C. D. Clarke, R. L. Howard, J. S. Strobl, *Biochem. Pharmacol.* **2004**, *68*, 1729–1738; k) A. Perzyna, F. Klupsch, R. Houssin, N. Pommery, A. Lemoine, J. P. Hénichart, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2363–2365; l) C. Portela, C. M. M. Afonso, M. M. M. Pinta, M. J. Ramos, *Bioorg. Med. Chem.* **2004**, *12*, 3313–3321; m) A. A. Joshi, S. S. Narkhede, C. L. Viswanathan, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 73–76; n) A. A. Joshi, C. L. Viswanathan, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2613–2617;

o) J. D. Wansi, M. A. Mesaik, D. D. Chiozem, K. P. Devkota, N. Gaboriaud-Kolar, M.-C. Lallemand, J. Wandji, M. I. Choudhary, N. Sewald, *J. Nat. Prod.* **2008**, *71*, 1942–1945; p) D. S. Bose, M. Idrees, N. M. Jakka, J. V. Rao, *J. Comb. Chem.* **2010**, *12*, 100–110.

[3] M. F. Grundon in *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1988**, vol. 32, pp. 341–439.

[4] a) G. H. Svoboda, G. H. Poore, P. J. Simpson, G. B. Boder, *J. Pharm. Sci.* **1966**, *55*, 758–768; b) B. Wolters, U. Eilert, *Planta Med.* **1981**, *43*, 166–174; c) L. K. Basco, S. Mitaku, A. L. Skaltsounis, N. Ravelomanantsoa, F. Tillequin, M. Koch, J. Le Bras, *Antimicrob. Agents Chemother.* **1994**, *38*, 1169–1171.

[5] a) T. Usui, Y. Tsubone, A. Tanaka, *J. Heterocycl. Chem.* **1985**, *22*, 849–852; b) A. Godard, J. M. Jacquelin, G. Queguiner, *J. Heterocycl. Chem.* **1988**, *25*, 1053–1054; c) V. S. Rao, M. Darbarwar, *Synth. Commun.* **1989**, *19*, 2713–2719; d) S. Yamaguchi, T. Yokoi, M. Yamada, H. Arai, Y. Uchiuzo, Y. Kawase, *J. Heterocycl. Chem.* **1990**, *27*, 1003–1005; e) K. C. Majumdar, A. K. Kundu, P. Biswas, *Heterocycles* **1999**, *51*, 2399–2406; f) M. C. Pirrung, F. Blume, *J. Org. Chem.* **1999**, *64*, 3642–3649; g) S. Venkataraman, D. K. Barange, M. Pal, *Tetrahedron Lett.* **2006**, *47*, 7317–7322.

[6] One-pot, three-component synthesis of saturated dihydrofuro[3,2-*c*]quinoline based on Povarov cycloaddition, see: a) L. S. Povarov, *Russ. Chem. Rev.* **1967**, *36*, 656–670; b) S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1996**, *118*, 8977–8978; c) Y. Ma, C. Qian, M. Xie, J. Sun, *J. Org. Chem.* **1999**, *64*, 6462–6467; d) B. Crousse, J. P. Byguy, D. Bonnet-Delpon, *J. Org. Chem.* **2000**, *65*, 5009–5013; e) R. A. Batey, D. A. Powell, A. Acton, A. J. Lough, *Tetrahedron Lett.* **2001**, *42*, 7935–7939; f) J. Barluenga, A. Mendoza, F. Rodriguez, F. J. Fananas, *Chem. Eur. J.* **2008**, *14*, 10892–10895; g) C. D. Smith, J. I. Gavrilyuk, A. J. Lough, R. A. Batey, *J. Org. Chem.* **2009**, *75*, 702–715; h) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598–4599; i) C. Wang, Z.-Y. Han, H.-W. Luo, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 2266–2269; j) M. Xie, X. Chen, Y. Zhu, B. Gao, L. Lin, X. Liu, X. Feng, *Angew. Chem. Int. Ed.* **2010**, *49*, 3799–3802.

[7] a) W. Du, D. P. Curran, *Org. Lett.* **2003**, *5*, 1765–1768; b) U. Bhoga, R. S. Mali, S. R. Adapa, *Tetrahedron Lett.* **2004**, *45*, 9483–9485; c) T. Godet, J. Bosson, P. Belmont, *Synlett* **2005**, 2786–2790; d) I. Aillaud, E. Bossharth, D. Conreaux, P. Desbordes, N. Monteiro, G. Balme, *Org. Lett.* **2006**, *8*, 1113–1116; e) T. Godet, C. Vaxelaire, C. Michel, A. Milet, P. Belmont, *Chem. Eur. J.* **2007**, *13*, 5632–5641; f) Z. Zhang, Q. Zhang, S. Sun, T. Xiong, Q. Liu, *Angew. Chem.* **2007**, *119*, 1756; *Angew. Chem. Int. Ed.* **2007**, *46*, 1726–1729.

[8] a) P. Cironi, J. Tulla-Puche, G. Barany, F. Albericio, M. Álvarez, *Org. Lett.* **2004**, *6*, 1405–1408; b) J. Su, J. Xiong, S. Liang, G. Qiu, X. Feng, H. Teng, L. Wu, X. Hu, *Synth. Commun.* **2006**, *36*, 693–699.

[9] For selected reviews on domino processes, see: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223–269; c) M. H. Filippini, J. Rodriguez, *Chem. Rev.* **1999**, *99*, 27–76; d) for a monograph, see: L. F. Tietze, G. Brasche, K. Gericke (Eds.), *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[10] a) J. Zhu, H. Bienaymé (Eds.), *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; for reviews, see: b) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–3329; c) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899–907; d) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* **2003**, 4104–4111; e) C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957–4980; f) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; g) D. Tejedor, F. Garcia-Tellado, *Chem. Soc. Rev.* **2007**, *36*, 484–491; h) I. Akritopoulou-Zane, S. W. Djuric, *Heterocycles* **2007**, *73*, 125–147; i) N. Isambert, R. Lavilla, *Chem. Eur. J.* **2008**, *14*, 8444–8454; j) L. F. Tietze, T. Kinzel, C. C. Brazel, *Acc. Chem. Res.* **2009**, *42*, 367–378; k) L. El Kaim, L. Grimaud, *Tetrahedron* **2009**, *65*, 2153–2171; l) J. D. Sunderhaus, S. F. Martin, *Chem. Eur. J.* **2009**, *15*, 1300–1308; m) B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463–472; n) B. A. Arndtsen, *Chem. Eur. J.* **2009**, *15*, 302–313; o) E. Godineau, Y. Landais, *Chem. Eur. J.* **2009**, *15*, 3044–3055; p) A. L. Wessjohann, D. G. Rivera, O. E. Vercillo, *Chem. Rev.* **2009**, *109*, 796–814; q) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235–5331; r) S. Sadjadi, M. M. Heravi, *Tetrahedron* **2011**, *67*, 2707–275; s) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246.

[11] A. Fayol, J. Zhu, *Angew. Chem.* **2002**, *114*, 3785; *Angew. Chem. Int. Ed.* **2002**, *41*, 3633–3635.

[12] For an account on the "substrate design approach" in the development of MCRs, see: a) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; for serendipity in MCR discovery, see, for example: b) H. Bienaymé, K. Bouzid, *Angew. Chem.* **1998**, *110*, 2349; *Angew. Chem. Int. Ed.* **1998**, *37*, 2234–2237; c) K. Groebke, L. Weber, F. Mehlin, *Synlett* **1998**, 661–663; d) C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.* **1998**, *39*, 3635–3638; e) D. Bonne, M. Dehkane, J. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 6926–6927; f) J.-M. Grassot, G. Masson, J. Zhu, *Angew. Chem.* **2008**, *120*, 961; *Angew. Chem. Int. Ed.* **2008**, *47*, 947–950; for the union principle in MCR development, see: g) A. Dömling, I. Ugi, *Angew. Chem.* **1993**, *105*, 634; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 563–564; h) N. Elders, D. van der Born, L. J. D. Hendrickx, B. J. J. Timmer, A. Krause, E. Janssen, F. J. J. de Kanter, E. Ruijter, R. V. A. Orru, *Angew. Chem.* **2009**, *121*, 5970; *Angew. Chem. Int. Ed.* **2009**, *48*, 5856–5859; mechanism-based design of MCRs, see: i) L. El Kaim, L. Grimaud, J. Oble, *Angew. Chem.* **2005**, *117*, 8175; *Angew. Chem. Int. Ed.* **2005**, *44*, 7961–7964; j) G. B. Giovenzana, G. C. Tron, S. D. Paola, I. G. Menegotto, T. Pirali, *Angew. Chem.* **2006**, *118*, 1117; *Angew. Chem. Int. Ed.* **2006**, *45*, 1099–1102.

[13] a) D. Bonne, M. Dekhane, J. Zhu, *Angew. Chem.* **2007**, *119*, 2537; *Angew. Chem. Int. Ed.* **2007**, *46*, 2485–2488; b) C. Lalli, M. J. Bouma, D. Bonne, G. Masson, J. Zhu, *Chem. Eur. J.* **2011**, *17*, 880–889.

[14] a) X. Sun, P. Janvier, G. Zhao, H. Bienaymé, J. Zhu, *Org. Lett.* **2001**, *3*, 877–880; b) E. González-Zamora, A. Fayol, M. Bois-Choussy, A. Chiaroni, J. Zhu, *Chem. Commun.* **2001**, 1684–1685; c) R. Gámez-Montaño, E. González-Zamora, P. Potier, J. Zhu, *Tetrahedron* **2002**, *58*, 6351–6358; d) P. Janvier, X. Sun, H. Bienaymé, J. Zhu, *J. Am. Chem. Soc.* **2002**, *124*, 2560–2567; e) A. Fayol, J. Zhu, *Org. Lett.* **2003**, *5*, 115–118; f) P. Janvier, M. Bois-Choussy, H. Bienaymé, J. Zhu, *Angew. Chem.* **2003**, *115*, 835; *Angew. Chem. Int. Ed.* **2003**, *42*, 811–814; g) D. Bonne, M. Dekhane, J. Zhu, *Org. Lett.* **2004**, *6*, 4771–4774; h) A. Fayol, J. Zhu, *Org. Lett.* **2004**, *6*, 115–118; i) A. Fayol, J. Zhu, *Org. Lett.* **2005**, *7*, 239–242; j) D. Bonne, M. Dekhane, J. Zhu, *Org. Lett.* **2005**, *7*, 5285–5288; k) A. Fayol, J. Zhu, *Tetrahedron* **2005**, *61*, 11511–11519; l) T. Pirali, G. C. Tron, J. Zhu, *Org. Lett.* **2006**, *8*, 4145–4148; m) A. Fayol, E. González-Zamora, M. Bois-Choussy, J. Zhu, *Heterocycles* **2007**, *73*, 729–742.

[15] For catalytic enantioselective Passerini-type reactions by using α-isocyanoacetamide, see: a) S.-X. Wang, M.-X. Wang, D.-X. Wang, J. Zhu, *Org. Lett.* **2007**, *9*, 3615–3618; b) S.-X. Wang, M.-X. Wang, D.-X. Wang, J. Zhu, *Angew. Chem.* **2008**, *120*, 394; *Angew. Chem. Int. Ed.* **2008**, *47*, 388–391; c) T. Yue, M.-X. Wang, D.-X. Wang, J. Zhu, *Angew. Chem.* **2008**, *120*, 9596; *Angew. Chem. Int. Ed.* **2008**, *47*, 9454–9457; d) T. Yue, M.-X. Wang, D.-X. Wang, G. Masson, J. Zhu, *Angew. Chem.* **2009**, *121*, 6845; *Angew. Chem. Int. Ed.* **2009**, *48*, 6717–6721.

[16] a) U. Schöllkopf, *Angew. Chem.* **1977**, *89*, 351; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 339–348; b) D. Hoppe, *Angew. Chem.* **1974**, *86*, 878; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 789–804; c) S. Marcaccini, T. Torroba, *Org. Prep. Proced. Int.* **1993**, *25*, 141–208; d) D. Van Leusen, A. M. Van Leusen, *Org. React.* **2001**, *57*, 417–666; e) M. Suzuki, K.-I. Nunami, T. Moriya, K.

Matsumoto, N. Yoneda, *J. Org. Chem.* **1978**, *26*, 4933–4935; f) R. S. Bon, C. Hong, M. J. Bouma, R. F. Schmitz, F. J. J. De Kanter, M. Lutz, A. L. Spek, R. V. A. Orru, *Org. Lett.* **2003**, *5*, 3759–3762; g) R. S. Bon, B. Van Vliet, N. E. Sprenkels, R. F. Schmitz, F. J. J. De Kanter, C. V. Stevens, M. Swart, F. M. Bickelhaupt, M. B. Groen, R. V. A. Orru, *J. Org. Chem.* **2005**, *70*, 3542–3553.

[17] For a review on the intramolecular Diels–Alder reaction of oxazoles and acetylenes, see: a) P. A. Jacobi, *Adv. Heterocycl. Nat. Prod. Synth* (Ed.: W. H. Pearson), JAI Press,, Greenwich, **1992**, vol. 2, pp. 251–298; b) M. Karpeiskii, M. Ya, V. L. Florent'ev, *Russ. Chem. Rev.* **1969**, *38*, 540–546; c) D. L. Boger, *Chem. Rev.* **1986**, *86*, 781–793.

[18] Ring-chain tautomerization of α-isocyanoacetates to oxazoles is well known, see: a) J. P. Chupp, K. L. Leschinsky, *J. Heterocycl. Chem.* **1980**, *17*, 705–709; b) I. Maeda, K. Togo, R. Yoshida, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1407–1410.

[19] Recent examples of oxazole synthesis: a) N. Elders, E. Ruijter, F. J. J. de Kanter, M. B. Groen, R. V. A. Orru, *Chem. Eur. J.* **2008**, *14*, 4961–4973; b) R. Scheffelaar, M. Paravidino, D. Muilwijk, M. Lutz, A. L. Spek, F. J. J. de Kanter, R. V. A. Orru, E. Ruijter, *Org. Lett.* **2009**, *11*, 125–128; c) J. Zhang, E. A. Polishchuk, J. Chen, M. A. Ciufolini, *J. Org. Chem.* **2009**, *74*, 9140–9150; d) T. Lechel, D. Lentz, H.-U. Reissig, *Chem. Eur. J.* **2009**, *15*, 5432–5435; e) P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem. Int. Ed.* **2011**, *50*, 8931–8935; f) for a recent review dealing with the synthesis of oxazoles, see: J. Zhang, P.-Y. Coqueron, M. A. Ciufolini, *Heterocycles* **2011**, *82*, 949–980 and references cited therein.

[20] These compounds are easily synthesized from commercially available cinnamate or by Sonogashira coupling, see: a) K. J. Schofield, J. C. E. Simpson, *J. Chem. Soc.* **1945**, 512–520; b) K. Sonogashira in *Metal Catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 203–229; c) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922.

[21] a) A. Dömling, *Curr. Opin. Chem. Biol.* **2000**, *4*, 318–323; b) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80; c) P. Tempest, *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 776–788; d) I. Akritopoulou-Zanze, *Curr. Opin. Chem. Biol.* **2008**, *12*, 324–331; e) A. Isidro-Llobet, T. Murillo, P. Bello, A. Cilibrizzi, J. T. Hodgkinson, W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6793–6798.

Received: October 27, 2011
Published Online: December 5, 2011

