

# Exploiting the Electrophilic and Nucleophilic Dual Role of Nitrile Imines: One-Pot, Three-Component Synthesis of Furo[2,3-*d*]pyridazin-4(5*H*)-ones

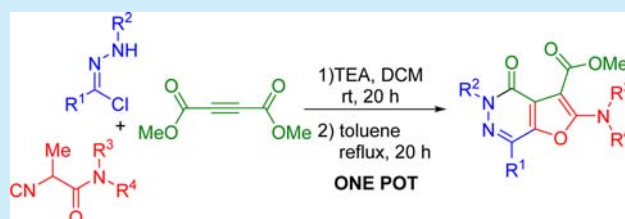
Mariateresa Giustiniano,<sup>\*,†</sup> Valentina Mercalli,<sup>‡</sup> Jussara Amato,<sup>†</sup> Ettore Novellino,<sup>†</sup> and Gian Cesare Tron<sup>\*,‡</sup>

<sup>†</sup>Dipartimento di Farmacia, Università degli Studi di Napoli "Federico II", via D. Montesano 49, 80131 Napoli, Italy

<sup>‡</sup>Dipartimento di Scienze del Farmaco, Università degli Studi del Piemonte Orientale "A. Avogadro", Largo Donegani 2, 28100 Novara, Italy

## Supporting Information

**ABSTRACT:** An expeditious multicomponent reaction to synthesize tetrasubstituted furo[2,3-*d*]pyridazin-4(5*H*)-ones is reported. In brief, hydrazoneyl chlorides react with isocyanacetamides, in the presence of TEA, to give 1,3-oxazol-2-hydrazones which, without being isolated, can react with dimethylacetylene dicarboxylate to afford furo[2,3-*d*]pyridazin-4(5*H*)-ones with an unprecedented level of complexity in a triple domino Diels–Alder/retro-Diels–Alder/lactamization reaction sequence.



The importance of the pyridazinone nucleus in medicinal chemistry is well validated by a plethora of biological activities as recently reviewed.<sup>1</sup> The bioactivity profiles range from cardiovascular and heart diseases<sup>2</sup> to antihypertensive, antithrombotic, antiinflammatory, and antiulcer activities.<sup>3</sup> Furthermore, some pyridazinone derivatives have shown potential as anticancer agents.<sup>4</sup> Although the syntheses of the pyridazinone nucleus per se are robust and well validated,<sup>5</sup> the syntheses of pyridazinones fused with other heterocycles still require efforts and improvements. For example, furo[2,3-*d*]pyridazin-4(5*H*)-one derivatives have shown potential in medicinal chemistry as immunomodulator, antiasthmatic, and thromboxane A2 synthase inhibitors,<sup>6</sup> but despite their pharmaceutical relevance, the reported synthetic approaches required several reaction steps followed by chromatographic purifications.

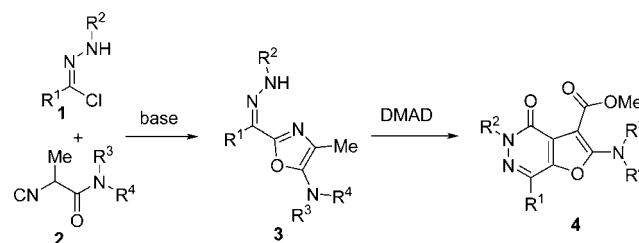
Over the last decades, the use of multicomponent reactions to build functionalized heterocyclic rings starting from acyclic precursors has received growing attention.<sup>7</sup> Indeed, the use of a multicomponent convergent process versus a divergent synthesis can be advantageous toward reducing the number of synthetic steps and sometimes allowing for the obtaining of never reported heterocyclic rings.<sup>7f,g</sup>

Recently, we have shown, for the first time, the productive use of the 1,3-dipolar species nitrile imine, generated in situ from hydrazoneyl chlorides, in a three-component reaction with carboxylic acids and isocyanides to afford the peptidomimetic aminocarbonyl *N*-acylhydrazones,<sup>8</sup> a class of compounds difficult to obtain with other strategies.<sup>9</sup> Despite their long history,<sup>10</sup> in our opinion, nitrile imines are still an unexplored class of compounds in multicomponent reactions. Indeed, they

can be simultaneously useful both as electrophilic partners for isocyanides and as nucleophilic terminus of reaction.

Stimulated by our first results with nitrile imines and in connection with our ongoing studies on the reactivity of  $\alpha$ -isocyanacetamides,<sup>11</sup> we envisaged a multicomponent synthesis of fully substituted furo[2,3-*d*]pyridazin-4(5*H*)-ones (4), starting from readily available hydrazoneyl chlorides 1 and  $\alpha$ -methylisocyanacetamides 2 (Scheme 1). The intermediate  $\alpha$ -

## Scheme 1. General Reaction Sequence To Obtain Furo[2,3-*d*]pyridazin-4(5*H*)-ones

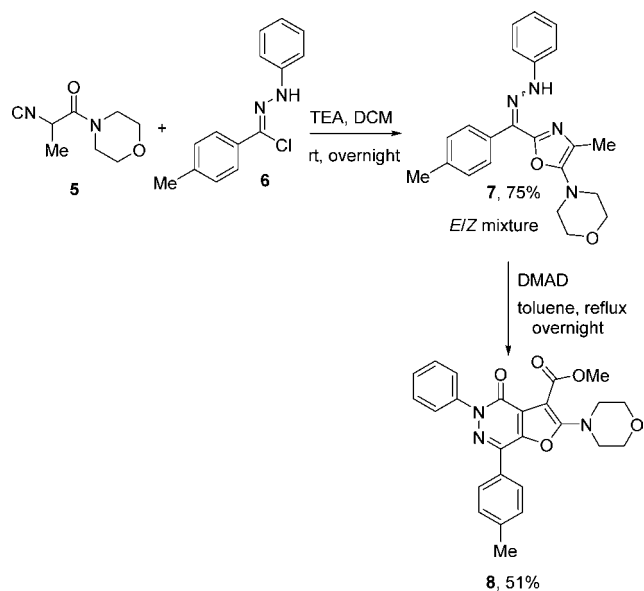


hydrazone-oxazole 3 obtained is then reacted in situ with dimethylacetylene dicarboxylate (DMAD), which should be able to trigger a triple-domino process consisting of a Diels–Alder cyclization, a [4 + 2]cycloreversion, and an intramolecular lactamization.

According to Scheme 2, 2-isocyano-1-morpholinopropan-1-one<sup>12</sup> (5) and the hydrazoneyl chloride (6) were mixed in

Received: June 22, 2015

Published: August 5, 2015

Scheme 2. Synthetic Scheme for the Synthesis of Furo[2,3-*d*]pyridazin-4(*5H*)-one (8)

dichloromethane in the presence of 1 equiv of TEA overnight at room temperature. Addition of isocyanide to nitrile imine is stereoselective, affording the *Z*-isomer.<sup>13</sup> Due to the low energy barrier required for the *Z* to *E* isomerism of this class of hydrazones, we detected a *Z/E* mixture of 1,3-oxazole-2-hydrazone (7) obtained in 75% yield after chromatographic column.<sup>14</sup> Subsequent reaction of 7 with 1 equiv of DMAD in toluene at reflux overnight afforded a novel fluorescent spot on TLC which, after purification and spectroscopic investigation, was shown to be the desired furo[2,3-*d*]pyridazin-4(*5H*)-one (8) obtained in 51% yield (Scheme 2).

After demonstrating the feasibility of this novel transformation, in a further advancement, we evaluated the possibility to perform the whole transformation in a one-pot, two-step domino fashion without isolating the 1,3-oxazole-2-hydrazone intermediate 7. Indeed, after monitoring its formation by TLC, the dichloromethane was evaporated and the crude reaction mixture was dissolved in toluene: by simply adding DMAD the reaction proceeded smoothly toward the formation of the furo[2,3-*d*]pyridazin-4(*5H*)-one (4). When different DMAD equivalents (1, 1.2, 1.5, and 2 equiv) were screened, a satisfactory yield of 45% was obtained when 2 equiv was used.

The proposed reaction mechanism is reported in Scheme 3. The hydrazonoyl chloride 6 formed in situ the dipolar nitrile imine 9, which was then attacked by the isocyanide carbon atom of isocyanoacetamide 5. Once the nitrilium ion 10 formed, it was intramolecularly intercepted by the oxygen of the tertiary amide to give the 1,3-oxazole-2-hydrazone 7. The latter was then able to attack the DMAD (11) triple bond to give the oxa-bridged intermediate 12 via Diels–Alder reaction, which after acetonitrile loss by means of a [4 + 2] cycloreversion and methanol loss by means of intramolecular lactamization gave the desired furo[2,3-*d*]pyridazin-4(*5H*)-one (8).

With these optimized one-pot reaction conditions in hand, we started to evaluate the scope of this transformation using different hydrazonoyl chlorides (6, 13–19) and isocyanoacetamides (5, 20–23) (Figure 1) and randomly combining them

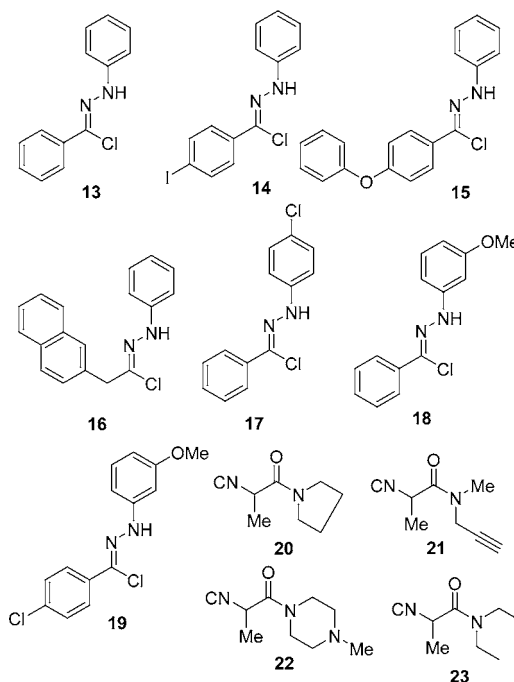
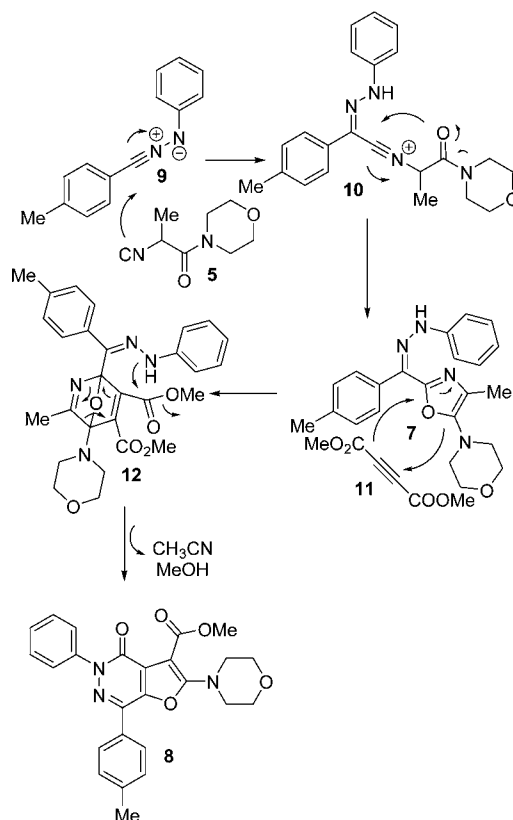
Scheme 3. Proposed Reaction Mechanism for the One-Pot Domino Formation of Furo[2,3-*d*]pyridazin-4(*5H*)-ones 4

Figure 1. Building blocks used.

in order to get a library of furo[2,3-*d*]pyridazin-4(*5H*)-ones (24–34) (Figure 2). Hydrazonoyl chlorides were readily synthesized in two steps starting from commercial carboxylic acids and aryl hydrazines (see the Supporting Information).

Yields ranged from 22 to 50% and were shown to be unaffected by the hydrazonoyl chloride substitution pattern as

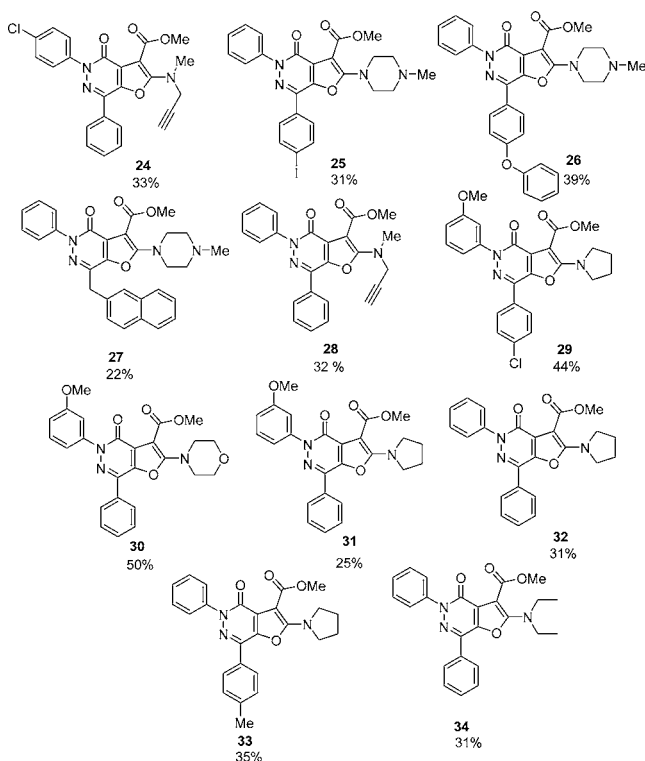


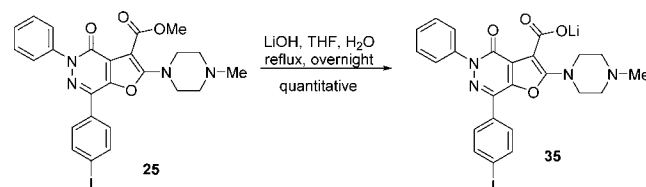
Figure 2. Library of synthesized furo[2,3-d]pyridazin-4(SH)-ones.

both electron-withdrawing chlorine or iodine atoms (14, 17, and 19, Figure 2), and electron-donor methoxy or phenoxy groups gave good yields (15, 18, and 19, Figure 2). Isocyanacetamides with an additional alkyne function, amenable to further derivatization (21, Figure 2) or a basic amine group (22, Figure 2), also worked well, allowing for the generation of widely decorated heterocycles. Notably, the yields are referred to a sequence of four different reactions (the formation of 1,3-oxazol-2-hydrazone, the Diels–Alder cyclization with DMAD, the [4 + 2] cycloreversion with the extrusion of acetonitrile, and the intramolecular lactamization with loss of methanol), indicating an average yield of 84–67% for each synthetic step. It is important to highlight that, to date, the chemistry of isocyanacetamides coupled with domino sequences has been mainly explored using aldehydes, imines, and acyl chlorides as electrophilic partners.<sup>15</sup> In this case, the use of hydrazoneyl chlorides allowed for the incorporation of one more nitrogen atom in the forming heterocyclic ring, giving access to a furo[2,3-d]pyridazinone scaffold not synthesizable with the previous strategies.

Notwithstanding its vinylogous carbamic nature, the ester function can also be easily hydrolyzed without affecting the pyridazinone moiety, providing an acid group amenable to further derivatization as reported in Scheme 4 for compound 35.

In conclusion, we reported a one-pot synthesis of fully substituted furo[2,3-d]pyridazin-4(SH)-ones, through a multi-component, one-pot sequence of four different reactions: oxazole formation, Diels–Alder cyclization, [4 + 2]-cycloreversion, and intramolecular lactamization. The reactivity of 1,3-dipolar species nitrile imines, in situ generated from hydrazoneyl chlorides, toward isocyanacetamides was explored here for the first time in a three-center, two-component reaction and in combination with a further sequence of

#### Scheme 4. Synthesis of the Furo[2,3-d]pyridazin-3-carboxylic Acid 35



postcondensation domino processes. This method constitutes a significant advancement over previously reported strategies<sup>16</sup> and is likely to facilitate deeper medicinal chemistry studies of this class of compounds.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01798.

Experimental procedures, spectroscopic data, copies of <sup>1</sup>H and <sup>13</sup>C spectra (PDF)

#### ■ AUTHOR INFORMATION

##### Corresponding Authors

\*E-mail: mariateresa.giustiniano@unina.it.

\*E-mail: giancesare.tron@pharm.unipmn.it.

##### Notes

The authors declare no competing financial interest.

#### ■ ACKNOWLEDGMENTS

Financial support from Università del Piemonte Orientale, Novara, and Università degli Studi “Federico II” Napoli, Italy, is acknowledged.

#### ■ REFERENCES

- (a) Asif, M. *Curr. Med. Chem.* **2012**, *19*, 2984–2991. (b) Máatyus, P. J. *Heterocycl. Chem.* **1998**, *35*, 1075–1089. (c) Chowdary, K. P. R.; Namrata, N. *Asian J. Chem.* **2011**, *23*, 1905–1910. (d) Bansal, R.; Thota, S. *Med. Chem. Res.* **2013**, *22*, 2539–2552.
- (a) Nomoto, Y.; Takai, H.; Nagashima, K.; Yao, K.; Yamada, K.; Kubo, K.; Ichimura, M.; Mihara, A.; Kase, H.; Ohno, T. *J. Med. Chem.* **1996**, *39*, 297–303. (b) Estevez, I.; Ravina, E.; Sotelo, E. *J. Heterocycl. Chem.* **1998**, *35*, 1421–1428.
- (a) Curran, W. V.; Ross, A. *J. Med. Chem.* **1974**, *17*, 273–281. (b) McEvoy, F. J.; Allen, G. R. *J. Med. Chem.* **1974**, *17*, 281–286. (c) Sircar, I.; Steffen, R. P.; Bobowski, G.; Burke, S. E.; Newton, R. S.; Weishaar, R.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1989**, *32*, 342–350.
- Prime, M. E.; Courtney, S. M.; Brookfield, F. A.; Marston, R. W.; Walker, V.; Warne, J.; Boyd, A. E.; Kairies, N. A.; von der Saal, W.; Limberg, A.; Georges, G.; Engh, R. A.; Goller, B.; Rueger, P.; Rueth, M. *J. Med. Chem.* **2011**, *54*, 312–319.
- (a) Boukharsa, Y.; Zaoui, Y.; Taoufik, J.; Ansar, M. *J. Chem. Pharm. Res.* **2014**, *6*, 297–310. (b) Hyeon Sung, G.; Ram Kim, B.; Lee, S.-G.; Kim, J.-J.; Yoon, Y.-J. *Curr. Org. Chem.* **2012**, *16*, 852–858. (c) Lee, S.-G.; Kim, J.-J.; Kim, H.-K.; Kweon, D.-H.; Kang, Y.-J.; Cho, S.-D.; Kim, S.-K.; Yoon, Y.-J. *Curr. Org. Chem.* **2004**, *8*, 1463–1480.
- Yamaguchi, M.; Maruyama, N.; Koga, T.; Kamei, K.; Akima, M.; Kuroki, T.; Hamana, M.; Ohi, N. *Chem. Pharm. Bull.* **1995**, *43*, 236–240.
- For reviews and books see: (a) Lygin, A. V.; De Meijere, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094–9124. (b) Rotstein, B. H.;

Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev.* **2014**, *114*, 8323–8359. (c) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083–3135. (d) Van der Heijden, G.; Ruijter, E.; Orru, R. V. A. *Synlett* **2013**, *24*, 666–685. (e) *Isocyanide Chemistry*; Nenajdenko, V. G., Ed.; Wiley–VCH: Weinheim, 2012; Chapters 11–13. (f) *Synthesis of Heterocycles via Multicomponent Reactions I*; Orru, R. V. A., Ruijter, E., Eds.; Springer: New York, 2010. (g) *Synthesis of Heterocycles via Multicomponent Reactions II*; Orru, R. V. A., Ruijter, E., Eds.; Springer: New York, 2010. Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235–5331.

(8) (a) Giustiniano, M.; Meneghetti, F.; Mercalli, V.; Varese, M.; Giustiniano, F.; Novellino, E.; Tron, G. C. *Org. Lett.* **2014**, *16*, 5332–5335.

(9) Moderhack, D. *Liebigs Ann. Chem.* **1989**, *1989*, 1271–1274.

(10) The first nitrile imine was synthesized by Huisgen and co-workers in 1959. See: Huisgen, R.; Seidel, M.; Sauer, J.; McFarland, J. W.; Wallbillich, G. *J. Org. Chem.* **1959**, *24*, 892–893.

(11) (a) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145–4148. (b) Pirali, T.; Tron, G. C.; Masson, G.; Zhu, J. *Org. Lett.* **2007**, *9*, 5275–5278. (c) Mossetti, R.; Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2010**, *12*, 820–823. (d) Giustiniano, M.; Mercalli, V.; Cassese, H.; Di Maro, S.; Galli, U.; Novellino, E.; Tron, G. C. *J. Org. Chem.* **2014**, *79*, 6006–6014. (e) Mossetti, R.; Caprioglio, D.; Colombano, G.; Tron, G. C.; Pirali, T. *Org. Biomol. Chem.* **2011**, *9*, 1627–1631.

(12) We have previously demonstrated the role of the leaving group in the cycloreversion step with acetonitrile being the best choice. See ref 11e.

(13) Hegarty, A. F. *Acc. Chem. Res.* **1980**, *13*, 448–454.

(14) It was possible to observe an increase of the *E* isomer amount when the spectra of **7** was registered at different times.

(15) (a) Sun, X.; Janvier, P.; Zhao, G.; Bienaymè, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877–880. (b) Janvier, P.; Sun, X.; Bienaymè, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560–2567. (c) Janvier, P.; Bienaymè, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4291–4294. (d) Fayol, A.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3633–3635. (e) Janvier, P.; Bois-Choussy, M.; Bienaymè, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 811–814. (f) Fayol, A.; Zhu, J. *Org. Lett.* **2004**, *6*, 115–118.

(16) (a) Robba, M.; Zaluski, M. C.; Roques, B. *Compt. Rend.* **1966**, *263*, 814. (b) Jones, R. G. *J. Am. Chem. Soc.* **1956**, *78*, 159–163. (c) Cartwright, M. W.; Parks, E. L.; Pattison, G.; Slater, R.; Sandford, G.; Wilson, L.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D. *Tetrahedron* **2010**, *66*, 3222–3227. (d) Karahan, E.; Koza, G.; Balci, M. *Helv. Chim. Acta* **2014**, *97*, 1487–1495.