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Synthesis of 1,2,4-Triazolines: Base-Catalyzed Hydrazination/Cyclization Cascade of α-Isocyano Esters and Amides

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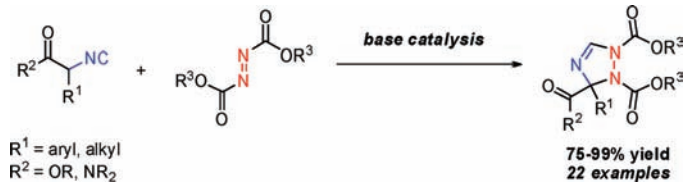
ABSTRACT



A convenient, efficient synthesis of 1,2,4-triazolines from α-isocyano esters/amides and azodicarboxylates is presented. The developed reaction cascade is based on a base-catalyzed hydrazination-type reaction followed by a subsequent cyclization providing the triazolines in good to excellent yields (75−99%). Phosphine-catalyzed and preliminary asymmetric phase-transfer catalysis approaches have also been investigated.

Nitrogen-containing heterocycles are of great importance in the pharmaceutical industry since they often exhibit interesting biological activities. The 1,2,4-triazole moiety constitutes the key structure of a wide range of compounds that have antiviral, anticancer, anti-inflammatory, and anticonvulsant properties.[1] Surprisingly, the saturated 1,2,4-triazolines belong to an underutilized class of heterocycles, whose potential biological properties remain largely unexplored. Recently, a convenient method for the synthesis of 1,2,4-triazolines using oxazolones and azodicarboxylates was described by Tepe et al.[2] The products accessed by this approach feature a quaternary C3 carbon atom containing a carboxylic acid functional group and an aryl/alkyl substituted C5 carbon atom (Figure 1, left). Other syntheses of related 1,2,4-triazole derivatives utilize oxazoles,[3] imidazopyridines,[4] or *N*-[(trimethylsilyl)methyl] iminium triflates.[5] Herein, we present an alternative synthesis from readily available α-isocyano esters/amides **1** and azodicarboxylates **2** leading to 1,2,4-triazolines **3** bearing a quaternary C3 carbon atom containing

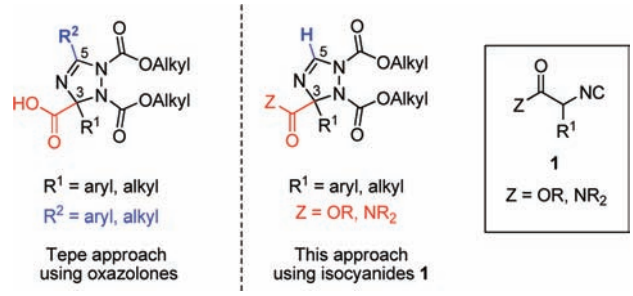


Figure 1. Analysis of 1,2,4-triazoline structures accessed by different nucleophiles.

(1) (a) Todoulou, O. G.; Papadaki-Valiraki, A. E.; Ikeda, S.; De Clercq, E. *Eur. J. Med. Chem.* **1994**, *29*, 611. (b) Bekircan, O.; Kahveci, B.; Kucuk, M. *Turk. J. Chem.* **2006**, *30*, 29. (c) Tandon, M.; Barthwal, J. P.; Bahalla, T. N.; Bhargava, K. P. *Indian J. Chem.* **1981**, *20B*, 1017. (d) Gulerman, N.; Rollas, S.; Kiraz, M.; Ekinci, A. C.; Vidin, A. *Farmaco* **1997**, *52*, 691.

(2) Saleem, R. S. Z.; Tepe, J. J. *J. Org. Chem.* **2010**, *75*, 4330.

(3) (a) Ibata, T.; Isogami, Y.; Tamura, H. *Chem. Lett.* **1988**, 1551. (b) Hassner, A.; Fischer, B. *Tetrahedron* **1989**, *45*, 3535. (c) Shi, X.; Ibata, T.; Suga, H.; Matsumoto, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3315. (d) Ibata, T.; Suga, H.; Isogami, Y.; Tamura, H.; Shi, X. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2998.

(4) Anderson, D. J.; Watt, W. *J. Heterocycl. Chem.* **1995**, *32*, 1525.

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an ester or amide functional group and a hydrogen substituent at C5 (Figure 1, right).

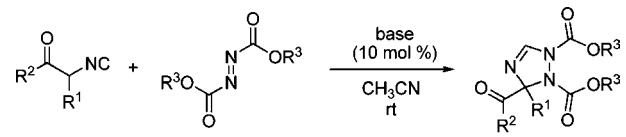
The unique properties of the isocyano group, which may function as both electrophile and nucleophile, have turned these compounds into indispensable reagents for organic synthesis.[6] Beyond the classical multicomponent Ugi and Passerini reactions,[7] the most important applications of isocyanides are in the synthesis of various heterocycles.[8] In particular, isocyano esters/amides have been employed as key building blocks for the syntheses of 1,3-azoles, azolines, pyrroles, pyrrolines, 1,2,4-triazoles, 2-imidazolidinones, 5,6-dihydro-4*H*-1,3-oxazines, and thiazines.[9] To the best of our knowledge, the reaction of α-isocyano ester derivatives with azodicarboxylates giving access to 1,2,4-triazolines has not been described to date.

Initially, we examined the base-catalyzed reaction employing isocyano esters (**1a**, R^1 = Ph; **1b**, R^1 = Bn), prepared from amino acids by formylation/dehydration protocols,[10] and commercially available di-*tert*-butyl azodicarboxylate (DTBAD) (see Supporting Information). Preliminary results showed organic bases such as Et_3N[11] for **1a** or 1,8-diazabicycloundec-7-ene (DBU)[11] for **1b** as the most promising catalysts providing the 1,2,4-triazolines **3** in excellent yields in CH_3CN at room temperature. The generality of this novel transformation was studied for a series of isocyano esters **1** and azodicarboxylates **2** [diethyl azodicarboxylate (DEAD, **2a**), diisopropyl azodicarboxylate (DIAD, **2b**), DTBAD **2c**, and dibenzyl azodicarboxylate (DBAD, **2d**)] using 10 mol % of base in CH_3CN (0.2 M) at room temperature (Table 1). Employing aryl/alkyl (R^1 = Ph, Bn, CH_2CH_2Ph, *i*-Pr, *i*-Bu) substituted isocyano esters (R^2 = OMe, OBn, O*t*-Bu) showed that the outcome of the reaction is relatively independent of substituents and the 1,2,4-triazolines **3a**−**n** were obtained in excellent yields (87−99%).

To further demonstrate the efficiency of the developed methodology, reactions were performed on a 2 mmol scale, as exemplified by the synthesis of **3e** (99%), **3f** (99%), and **3g** (96%) in excellent yields.

Competition experiments[12] revealed that DBAD is the most reactive azodicarboxylate counterpart in the present reaction conditions, which is in accordance with recent investigations by Mayr on the electrophilicities of azodicarboxylates (Bn > Et > *i*-Pr > *t*-Bu).[13]

Table 1. Scope of the Synthesis of 1,2,4-Triazolines **3** from Isocyano Esters[a]



1 **2** **3**

entry	R^1	R^2	**1**	R^3	base	yield (%)[b]
1	Ph	OMe	**1a**	*t*-Bu	Et_3N	**3a:** 99
2	Bn	OMe	**1b**	Et	DBU	**3b:** 98
3	Bn	OMe	**1b**	*t*-Bu	DBU	**3c:** 99
4	Bn	OBn	**1c**	Et	DBU	**3d:** 93
5	Bn	OBn	**1c**	*t*-Bu	DBU	**3e:** 99
6	Bn	O*t*-Bu	**1d**	Et	DBU	**3f:** 95
7	Bn	O*t*-Bu	**1d**	*i*-Pr	DBU	**3g:** 94
8	Bn	O*t*-Bu	**1d**	*t*-Bu	DBU	**3h:** 92
9	Bn	O*t*-Bu	**1d**	Bn	DBU	**3i:** 87
10	CH_2CH_2Ph	O*t*-Bu	**1e**	*t*-Bu	DBU	**3j:** 93
11	*i*-Pr	O*t*-Bu	**1f**	*t*-Bu	DBU	**3k:** 99
12	*i*-Bu	OBn	**1g**	*t*-Bu	DBU	**3l:** 95
13	*i*-Bu	O*t*-Bu	**1h**	*i*-Pr	DBU	**3m:** 93
14	*i*-Bu	O*t*-Bu	**1h**	*t*-Bu	DBU	**3n:** 92

[a] Reactions performed at 0.25 mmol scale of **1** in CH_3CN (0.2 M). Reation time typically 18 h (see Supporting Information). [b] Isolated by flash chromatography.

The importance of amide bonds in biologically active molecules[14] and the interest for improved understanding of bioactive conformations have stimulated the synthesis of new constrained peptidomimetics based on heterocyclic motives.[15] Therefore, the protocol was expanded to include isocyano amides, prepared by aminolysis/alkylation protocols.[16]

The acidity of isocyano amides differ considerably from their ester analogues, and their reactivity profile (isocyano group vs α-carbanion) is often governed by steric constrains, reaction conditions, and the combination of substrates.[17]

To our delight, preliminary studies using **1i** (R^1 = Ph, R^2 = morpholinyl) and **1j** (R^1 = Bn, R^2 = morpholinyl) with DTBAD employing the optimized conditions for isocyano esters (10 mol % of DBU in CH_3CN) afforded the 1,2,4-triazolines (**3o**, **3r**) in excellent yields, 99% and 98%, respectively, at room temperature (see Supporting Information). Interestingly, when Et_3N was used in combination with **1i**, an inseparable mixture of products was obtained. The scope of the reaction was then evaluated for a series of isocyano amides **1** and azodicarboxylates **2** (Table 2). By

(5) Tsuge, O.; Hatta, T.; Tashiro, H.; Maeda, H. *Heterocycles* **2001**, *55*, 243.

(6) For a general review, see: (a) Suginome, M.; Ito, Y. In *Science of Synthesis*, Vol. 19; Murahashi, S.-I., Ed.; Thieme: Stuttgart, 2004; p 445.

(7) For general reviews on multicomponent reactions, see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

(8) For a recent review, see: Lygin, A. V.; Meiere, A. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094.

(9) For a general review, see: Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.

(10) Hong, R. S.; Bouma, M. J.; Schmitz, R. F.; Kanter, F.; Lutz, M.; Spek, A. L.; Orru, R. *Org. Lett.* **2003**, *5*, 3759.

(11) Rodima, T.; Kaljurand, I.; Pihl, A.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2002**, *67*, 1873. pK_{BH+} in CH_3CN: Et_3N (18.8), DBU (24.2), TBD (26.0).

(12) **1d** (R^1 = Bn, R^2 = O*t*-Bu) + DBAD (1.2 equiv) + DTBAD (1.2 equiv) → **3i** (major, > 90%).

(13) Kanzian, T.; Mayr, H. *Chem.—Eur. J.* **2010**, *16*, 11670.

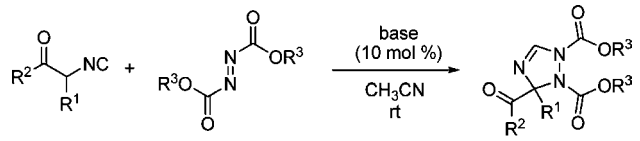
(14) For example, see: MacMillan, K. S.; Boger, D. L. *J. Med. Chem.* **2009**, *52*, 5771.

(15) For example, see: Petit, S.; Fruit, C.; Bischoff, L. *Org. Lett.* **2010**, *12*, 4928.

(16) Housseman, C.; Zhu, J. *Synlett* **2006**, *11*, 1777.

(17) For examples on multicomponent reactions giving access to different heterocycles, see: (a) Elders, N.; Ruijter, E.; Kanter, F. J. J. D.; Groen, M. B.; Orru, R. V. A. *Chem.—Eur. J.* **2009**, *15*, 6096. (b) Elders, N.; Ruijter, E.; Kanter, F. J. J. D.; Janssen, E.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Chem.—Eur. J.* **2009**, *15*, 6096. (c) Mossetti, R.; Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2010**, *12*, 820.

Table 2. Scope of the Synthesis of 1,2,4-Triazolines **3** from Isocyano Amides[a]



1 2 3

entry	R^1	R^2	1	R^3	base	yield (%)[b]
1	Ph	morpholinyl	**1i**	*t*-Bu	DBU	**3o:** 99
2	Bn	morpholinyl	**1j**	Et	DBU	**3p:** 89
3	Bn	morpholinyl	**1j**	*i*-Pr	DBU	**3q:** 94
4	Bn	morpholinyl	**1j**	*t*-Bu	DBU	**3r:** 98
5	Bn	morpholinyl	**1j**	Bn	TBD[c]	nr
6	*i*-Bu	morpholinyl	**1k**	*t*-Bu	DBU[d]	**3s:** 75
7	H	pyrrolidinyl	**1l**	*t*-Bu	DBU	**3t:** 79
8	Bn	pyrrolidinyl	**1m**	*t*-Bu	TBD[c]	**3u:** 90
9	*p*-BrC_6H_4	pyrrolidinyl	**1n**	*t*-Bu	TBD[c]	**3v:** 93
10	*i*-Bu	pyrrolidinyl	**1o**	*t*-Bu	TBD[c]	nr

[a] Reactions performed at 0.25 mmol scale of **1** in CH_3CN (0.2 M). Reation time typically 18 h (see Supporting Information). [b] Isolated by flash chromatography. [c] Reaction perfomed with 20 mol % of TBD. [d] Reaction perfomed with 20 mol % of DBU.

employing DEAD, DIAD, and DTBAD, the corresponding 1,2,4-triazolines **3o**−**r** were obtained in excellent yields (89−99%, entries 1−4). However, the more electrophilic DBAD remained unreactive toward the nucleophilic addition of **1j**, even when employing 20 mol % of 1,5,7-triazabicyclo(4.4.0)dec-5-ene (TBD)[11] (entry 5), suggesting that the initial quatenary C−N bond formation may be strongly hindered by steric bulk around the isocyano acetamide and azodicarboxylate N=N bond. When the benzyl group was exchanged for a branched isobutyl chain, 20 mol % of DBU were required and product **3s** was obtained in 75% yield (entry 6). Pyrrolidinyl amides were also investigated, and product **3t** with a hydrogen substituent was obtained in 79% yield (entry 7). When employing α-substituted pyrrolidinyl amides slightly modified reaction conditions [TBD (20 mol %), azodicarboxylate (2 equiv) in CH_3CN (0.3 M)] were required. Benzyl substituted pyrrolidine derivatives **1m,n** afforded the 1,2,4-triazolines **3u,v** in 90 and 93% yield, respectively (entries 8,9). Attempts to incorporate a branched isobutyl chain (**1o**) were unsuccessful (entry 10).

The reaction is believed to involve a base-catalyzed hydrazination via nucleophilic attack of deprotonated isocyanide **1** to the azodicarboxylate **2**, followed by a 5-*endo*-dig ring closure of intermediate **A** to give the 1,2,4-triazoline **3** as outlined in Scheme 1. However, a concerted [2 + 3]-cycloaddition of base-activated **1** with the azodicarboxylate **2**, followed by protonation of the resulting anion at C5, cannot be excluded.

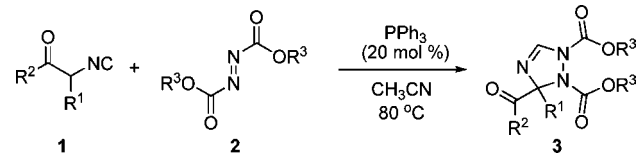
Kolasa and Miller have reported the synthesis of few triazolines from *N*-acyl glycine esters utilizing Mitsunobu reaction conditions PPh_3/DIAD.[18] The mechanism may involve the Huisgen zwitterion[19] acting as a base for the initial abstraction of the relatively acidic α-proton. Inspired

Scheme 1. Proposed Mechanism

1 A 3

by this study, we decided to explore an alternative PPh_3-promoted reaction.[20] To our delight, using stoichiometric or substoichiometric amounts of PPh_3 (30−100 mol %), the model reaction between isocyano esters **1** and azodicarboxylates **2** proceed very rapidly affording 60−80% conversions after a few minutes.[21] Finally, performing the reaction with 20 mol % of PPh_3 at 80 °C afforded full conversions in 3−18 h. As outlined in Table 3, the isolated yields were lower

Table 3. Phosphine-Catalyzed Examples[a]



1 2 3

entry	R^1	R^2	1	R^3	yield (%)[b]
1	Bn	O*t*-Bu	**1d**	Et	**3f:** 73
2	Bn	O*t*-Bu	**1d**	Bn	**3i:** 80
3[c]	Bn	OMe	**1b**	Bn	**3w:** 91
4	Bn	morpholinyl	**1j**	*t*-Bu	**3r:** 70[d]
5	Bn	morpholinyl	**1j**	Bn	nr

[a] Reactions performed at 0.25 mmol scale of **1** in CH_3CN (0.2 M). Reation time typically 18 h (see Supporting Information). [b] Isolated by flash chromatography. [c] Reaction performed with 10 mol % of PPh_3. [d] Isolated as a mixture with isocyano amide **1j**.

than those obtained using base-catalyzed conditions (73−91%, entries 1−3). As in the base-catalyzed system, the reactivity profile of **1** seems to correlate with the α-acidity.[22] Moreover, the addition of isocyano amide **1j** to DTBAD was slower and did not reach full conversion (entry 4, Table 2 vs Table 3).

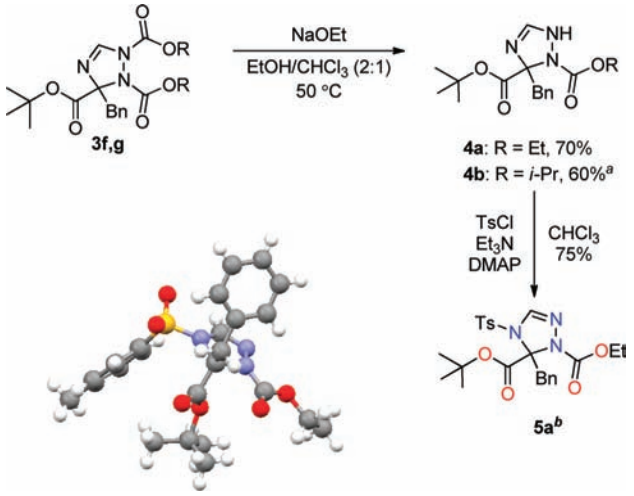
It is believed that the PPh_3-catalyzed reaction may involve Huisgen zwitterions as catalytic species,[23] as observed by

(18) Kolasa, T.; Miller, M. J. *Tetrahedron Lett.* **1988**, *29*, 4661.
(19) Reviews on zwitterions in C−C and C−N bond-forming reactions: (a) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (b) Nair, V.; Biju, A. T.; Mathew, S. C.; Babu, B. P. *Chem.—Asian J.* **2008**, *3*, 810.
(20) Review on nucleophile phosphine organocatalysis: Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.
(21) The reactions do not reach full conversions.
(22) Isocyano esters are more reactive than isocyano amides. For examples, see: (a) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560. (b) Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485.

^{1}H NMR and ^{31}P NMR spectroscopy (see Supporting Information), although the exact role of these species in the present system is not known.[24]

To highlight the synthetic potential of the 1,2,4-triazolines **3**, their mono-deprotection into **4** is presented in Scheme 2.

Scheme 2. Mono-deprotection of 1,2,4-Triazolines **3**



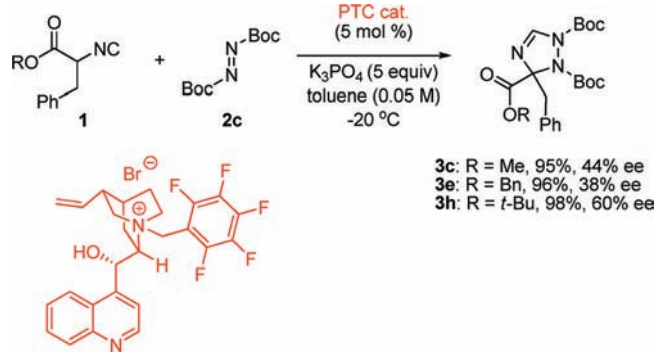
[a] Yield based on recovered starting material. [b] For X-ray crystal structure of compound **5a** (C gray, H white, O red, N blue, S yellow).

Performing the reaction with NaOEt (3 equiv) in a EtOH/$CHCl_3$ (2:1) mixture[25] at 50 °C afforded the mono-deprotected heterocycles **4a** and **4b** in 70 and 60% yield, respectively.

The product **4a** resulting from the attack of the ethoxide to the more accessible (N1) was transformed into **5a** using standard tosylation conditions. The structure of **5a** was verified by X-ray crystallography as depicted in Scheme 2.[26]

Next, we investigated the asymmetric version of this new reaction for the synthesis of enantiomerically enriched 1,2,4-triazolines **3**. By employing phase-transfer conditions (K_3PO_4-toluene) and a catalyst derived from cinchonine, triazolines **3c,e,h** were obtained in excellent yields (>95%) and moderate enantioselectivities (up to 60% ee for **3h**) as shown in Scheme 3.

Scheme 3. Synthesis of Optically Enriched 1,2,4-Triazolines **3** Using Asymmetric Phase-Transfer Catalysis



In conclusion, we have developed a new base-catalyzed hydrazination/cyclization cascade reaction of readily available isocyano esters/amides and azodicarboxylates for the synthesis of novel 1,2,4-triazolines bearing a quaternary C3 stereogenic center containing an ester or amide functional group. The synthetic procedure proved to be general, operationally simple, and high-yielding. We have also demonstrated an alternative PPh_3-catalyzed approach, which may expand the perspectives for developing new reactions using the combination of phosphines-azodicarboxylates. Finally, preliminary studies of the asymmetric synthesis of **3** using phase-transfer catalysis were described.

Acknowledgment. This research was made possible by the Carlsberg Foundation and OChem Graduate School. D.M. and I.M. thank the Ministerio de Ciencia e Innovacion of Spain for postdoctoral and predoctoral fellowships. Thanks are expressed to Helle Svendsen for performing X-ray analysis.

Supporting Information Available: Detailed experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102812C

(23) Hong, D.; Zhu, Y.; Lin, X.; Wang, Y. *Tetrahedron* **2010**, doi: 10.1016/j.tet.2010.11.043.

(24) For example, formation of radicals in the Mitsunobu reaction has been observed: Camp, D.; Hanson, G. R.; Jenkins, I. D. *J. Org. Chem.* **1995**, *60*, 2977.

(25) (a) Reactions performed in neat alcohol resulted in decomposition of starting material. (b) Using NaOMe (4 equiv, 0.5 M solution) in MeOH/$CHCl_3$ (2:1) at 50 °C afforded **4a** in 48% yield.

(26) CCDC-801217 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.