ORGANIC LETTERS

2010
Vol. 12, No. 17
3942−3945

Synthesis of 5-Amino-oxazole-4-carboxylates from α-Chloroglycinates

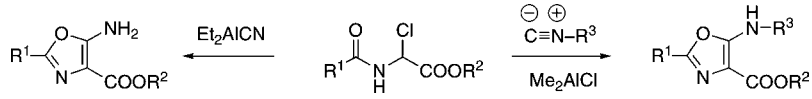
Jianmin Zhang,[†] Pierre-Yves Coqueron,[‡,§] Jean-Pierre Vors,[‡] and Marco A. Ciufolini*[,†]

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Canada, and Bayer CropScience SA, 14-20 Rue Pierre Baizet, 69009 Lyon, France

ciufi@chem.ubc.ca

Received July 21, 2010

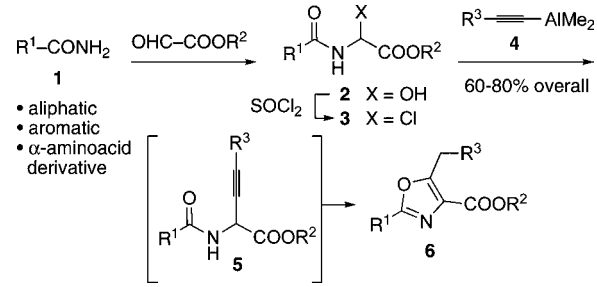
ABSTRACT



Aluminum-based Lewis acids are effective promoters of the condensation of α-chloroglycinates with isonitriles or with cyanide ion, leading to the formation of 5-amino-oxazoles.

An oxazole-forming reaction devised in our laboratories[1] proceeds through the condensation of an aluminum acetylide, **4**, with an α-chloroglycinate **3**, available in high yield from a generic primary amide **1** by addition to a glyoxylate ester[2] and chlorination of the intermediate **2** with $SOCl_2$ (Scheme 1). Applications have been demonstrated in total syntheses of muscoride A[1] and siphonazoles,[3] as well as in the preparation of various oxazole building blocks.[4] In the latter connection, ongoing research revealed a need for a family of 5-alkylamino derivatives of 2-alkyloxazole-4-carboxylates. The work of Deyrup[5] suggested that an avenue to 5-amino-oxazoles might become available if the acetylenic nucleophile in the chemistry of Scheme 1 were to be replaced with an isonitrile or even with a cyanide ion (Scheme 2; cf. **3** → **12**−**13**). Of course, the use of isonitriles as components of oxazole syntheses is well documented. Noteworthy examples of this chemistry are apparent from recent work by Zhu. What may be rightfully described as the Zhu oxazole synthesis involves the addition of isocyanoacetamides to aldehydes or imines, leading to products **9** (Scheme 2).[6] Enantioenriched products (cf. the starred C atom in **9**) emerge in the presence of chiral catalysts.[6d−f] A variant of the Zhu reaction recently disclosed by Yu yields 5-amino-oxazoles **11** upon addition of cyanoacetamides to in situ-generated carbalkoxyketenes **10**.[7] A somewhat related transformation entails the addition of the anion of isocy-

Scheme 1. Oxazole Formation from α-Chloroglycinates

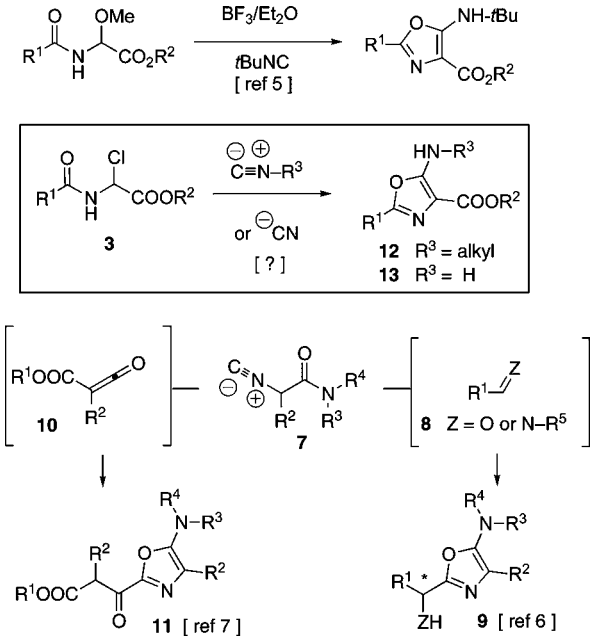


[†] University of British Columbia.
[‡] Bayer CropScience SA.
[§] Portions of this work are taken from the Ph.D. dissertation of P.Y.C, Université Claude Bernard Lyon I, 2001.

(1) Coqueron, P. Y.; Didier, C.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1411. This paper provides a bibliography of oxazole-forming reactions through early 2003.
(2) (a) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863. (b) Ben-Ishai, D.; Sataty, I.; Bernstein, Z. *Tetrahedron* **1976**, *32*, 1571. (c) Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 881.
(3) Zhang, J.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 2389.
(4) (a) Chau, J.; Zhang, J.; Ciufolini, M. A. *Tetrahedon Lett.* **2009**, *50*, 6163. (b) Zhang, J.; Polishchuk, E. A.; Chen, J.; Ciufolini, M. A. *J. Org. Chem.* **2009**, *74*, 9140.
(5) Deyrup, J. A.; Killion, K. K. *J. Heterocycl. Chem.* **1972**, *9*, 1045.

10.1021/ol101704r
Published on Web 08/10/2010

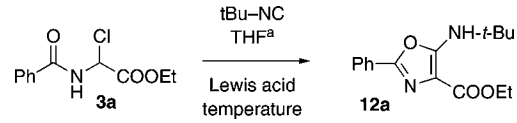
Scheme 2. Formation of Oxazoles from Isonitrile Educts



anoacetamide to an isocyanate.[8] It is apparent from Scheme 2 that the hypothetical conversion of **3** into **12**−**13** differs in outcome from other isonitrile-based avenues to 5-amino-oxazoles. Accordingly, it would nicely complement such alternative constructions. We also note that several other methods for 5-amino-oxazole synthesis do not employ isonitrile building blocks, relying instead on the cyclization of α-amidonitriles[9] and related reactions,[10] on the cyclo-dehydration of α-amido-amides,[11] or upon Cornforth-type rearrangements.[12]

The feasibility of the desired reaction was explored by studying the condensation of chloroglycinate **3a** with *tert*-butylisonitrile leading to **12a** (Table 1). In the absence of promoters, the two components failed to combine, prompting us to examine the effect of basic or acidic catalysts on the reaction. Compounds **3** are sensitive to the action of bases. Thus, exposure of **3a**, with or without an isonitrile, to the action of Et_3N or K_2CO_3 at 0 °C in THF induced rapid formation of intractable polymeric materials.

Table 1. Effect of the Lewis Acid Catalysts in the Reaction of **3a** with *tert*-Butylisonitrile



entry	Lewis acid	temperature/°C	yield[b]
a	$AlCl_3$	0	–
b	ZnI_2	0	27
c	$ZnCl_2$	0	48
d	$ZnCl_2$	25	66
e	$ZnCl_2$	reflux	49
f	$EtAlCl_2$	25	55
g	Me_2AlCl	25	69

[a] Typical procedure: the Lewis acid (1−3 equiv) was added to a solution of **3a** (0.5 mmol) and of *tert*-butyl isonitrile (1.5 mmol) in THF. [b] After column chromatography.

By contrast, particular halophilic Lewis acids were effective catalysts for the reaction (Table 1). No desired product was obtained when the substrates were combined in the presence of $AlCl_3$, while ZnI_2 afforded **12a** in modest yield. Better results were obtained with $ZnCl_2$. The process became more efficient at rt, while increasing the temperature to reflux had an adverse effect. However, Me_2AlCl at room temperature proved to be superior to $ZnCl_2$ in that it provided cleaner products. Yields of the desired oxazole **12a** were highest when 3 equiv each of isonitrile and Lewis acid promoter were employed.

This finding prompted us to examine the condensation of various permutations of chloroglycinates and isonitriles. Pertinent results are summarized in Table 2. It is apparent that the reaction proceeds in uniformly satisfactory yield, even though the yields of 2-methyloxazoles such as **12f** were consistently lower than those of its congeners. Valine-derived chloroglycinate **3i** provided the corresponding oxazole **12i** with no erosion of optical purity.

While at this time we favor (air-sensitive) Me_2AlCl as the promoter, the safer $ZnCl_2$ enabled the conduct of reactions that seemed to be amenable to automatization using a system such as the Chemspeed robot. This instrument, essentially a dispenser of liquids, would combine THF solutions of $ZnCl_2$, isonitriles, and chloroglycinates, and then perform an extractive workup and purify the crude products by HPLC-MS.[13]

Two aspects of this effort merit comment. First, the size of the library thus generated was of no import at this juncture. Indeed, our objective was to demonstrate the

(6) (a) Sun, X.; Janvier, J.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877. (b) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560. (c) Janvier, P.; Bois-Choussy, M.; Bienaymé, H.; Zhu, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 811. (d) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Org. Lett.* **2007**, *9*, 3615. (e) Yue, T.; Wang, M. X.; Wang, D. X.; Masson, G.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6717. (f) Yue, T.; Wang, M. X.; Wang, D. X.; Masson, G.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 8396. Related reactions: (g) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145. (h) Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2485.

(7) Wu, J.; Chen, W.; Hu, M.; Zou, H.; Yu, Y. *Org. Lett.* **2010**, *11*, 616.

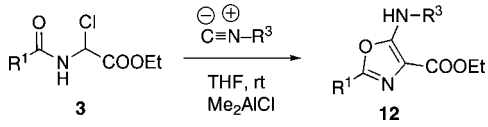
(8) Daniel, M.; Rizvi, R. K.; Kaminski, J. J. *Heterocycles* **1987**, *26*, 651.

(9) (a) Cook, A. H.; Hunter, G. D. *J. Chem. Soc.* **1952**, 3789. (b) Mandal, S.; Li, W. T.; Bai, Y.; Shablykin, O. V.; Brovarets, V. S.; Drach, B. S. *Russ. J. Gen. Chem.* **2007**, *77*, 1308. (c) Carreiras, M. C.; Eleuterio, A.; Dias, C.; Brito, M. A.; Brites, D.; Marco-Contelles, J.; Gomez-Sanchez, E. *Heterocycles* **2007**, *71*, 2249. (d) Robertus, J. D.; Kerwin, S. M. *Beilst. J. Org. Chem.* **2008**, *4*. http://www.beilstein-journals.org/bjoc/content/provisional/1860-5397-4-26.pdf.

(10) (a) Golovchenko, A. V.; Pilyo, S. G.; Brovarets, V. S.; Chernega, A. N.; Drach, B. S. *Russ. J. Gen. Chem.* **2005**, *75*, 425. (b) Golovchenko, A. V.; Pilyo, S. G.; Brovarets, V. S.; Chernega, A. N.; Drach, B. S. *Synthesis* **2003**, 2851. (c) Drach, B. S.; Mis'kevich, G. N.; Martynyuk, A. P. *Zh. Org. Khim.* **1978**, *14*, 508.

(11) (a) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Dettori, G. *Eur. J. Org. Chem.* **2000**, 3217. (b) Elliott, G. I.; Fuchs, J. R.; Blagg, B. S. J.; Ishikawa, H.; Tao, H.; Yuan, Z.-Q.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10589.

Table 2. 5-Alkylamino-oxazoles Obtained by the New Method



entry	R^1	R^3	yield[b]
a	Ph	*tert*-Bu	69
b	Ph	*n*-Bu	85
c	Ph	*cyclo*-C_6H_{11}	75
d	Ph	$PhCH_2$	78
e	Ph	$Ph(CH_2)_2$	61
f	Me	*n*-Bu	52
g	*cyclo*-C_6H_{11}	*n*-Bu	77
h	$PhCH_2$	*n*-Bu	56
i	*i*-Pr, PhtN	*n*-Bu	74

[a] General procedure: commercial Me_2AlCl (1.0 M in hexanes, 1.5 mL, 1.5 mmol) was added to a stirred solution of **3** (0.5 mmol) and isonitrile (1.5 mmol) in THF (1.5 mL), at rt. After 24 h, the mixture was quenched with aqueous saturated $NaHCO_3$ solution (5 mL) and extracted with EtOAc (5 mL × 3). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (30% EtOAc/hexanes in all cases). [b] After column chromatography.

feasibility of automating the new avenue to 5-amino-oxazoles. Second, yields of end products were also of marginal importance. The extractive workup performed by the robot is nowhere near as efficient as that executed by a human operator; but again, the goal here was to prove a point. What mattered was purity.

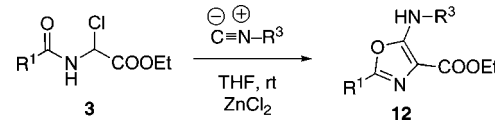
We arbitrarily chose to count as successful those reactions that afforded end products of a purity greater than 85% (HPLC-MS) in yields greater than 10%. These criteria reflect common boundary conditions applied during screening of new synthetic compounds for possible biological activity. The results of a parallel synthesis carried out with 5 chloroglycinates and 5 isonitriles are summarized in Table 3. Check marks indicate a successful reaction according to the foregoing criteria. It is apparent that two-thirds of the reactions were successful.

At this juncture, we turned to a study of the reaction of **3** with cyanide ion, in the interest of reaching amino-oxazoles **13** (cf. Table 4). Exposure of the chloroglycinates to KCN, $Zn(CN)_2$, $ZnCl_2$/KCN, $ZnCl_2$/TMSCN, and Et_3N/KCN in THF, at rt or reflux, failed to give any of the desired product. However, efficient conversion of **3** into **13** was achieved upon

(12) (a) Turchi, I. J.; Maryanoff, C. A. *Synthesis* **1983**, 837. (b) Nolt, M. B.; Smiley, M. A.; Varga, S. L.; McClain, R. T.; Wolkenberg, S. E.; Lindsley, C. W. *Tetrahedron* **2006**, *62*, 4698.

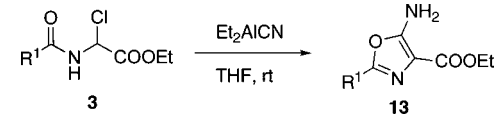
(13) In principle, the robot could also generate the chloroglycinates via the reaction of an amide with a glyoxylic ester, followed by treatment of the adduct with $SOCl_2$. However, safety and corrosion issues associated with the use of the latter reagent dissuaded us from carrying out this sequence on the Chemspeed instrument.

Table 3. Automated Preparation of a Library of 5-Amino-oxazoles (Chemspeed Robot)



R^1 ⇩ / R^3 ⇨	*tert*-Bu	*n*-Bu	*cyclo*-C_6H_{11}	$PhCH_2$	2,6-Me_2-C_6H_3
Ph	--	√	--	√	√
Me	--	√	--	√	√
cyclo-C_6H_{11}	√	--	--	√	√
2-Me-C_6H_4	√	--	√	√	√
2,6-F_2-C_6H_3	--	√	--	√	√

Table 4. 5-Amino-oxazoles Obtained by the New Method



entry	R^1	yield[b]
a	Ph	86
b	Me	36
c	*cyclo*-C_6H_{11}	76
d	$PhCH_2$	69
e	*i*-Pr, PhtN	74

[a] General procedure: commercial Et_2AlCN (1.0 M in toluene, 1.5 mL, 1.5 mmol) was added to a stirred solution of **3** (0.5 mmol) in THF (1.5 mL) at rt. After 24 h, the mixture was quenched with aqueous saturated $NaHCO_3$ solution (5 mL) and extracted with EtOAc (5 mL × 3). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (see Supporting Information for details). [b] After column chromatography.

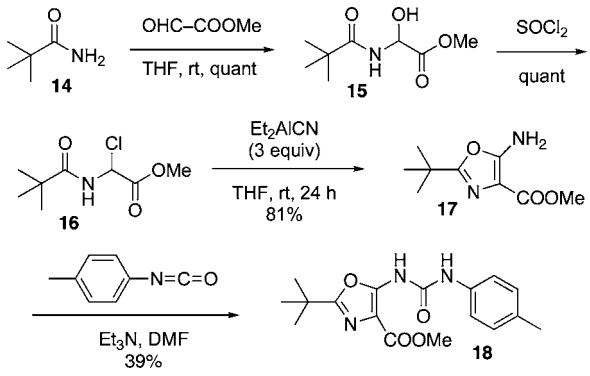
treatment with 3 equiv of Et_2AlCN (Nagata reagent)[14] in THF at rt. Representative examples of this transformation appear in Table 4. Once again, a diminshed yield was recorded in the 2-methyloxazole series (cf. **13b**).

Amino-oxazoles **13** are valuable building blocks for the asssembly of bioactive agents. As a simple application of the newly established route to these heterocycles, Scheme 3 details an avenue to oxazolylurea **18**, which is a moderately potent inhibitor of Raf kinase[15] and consequently an interesting starting point for the development of anticancer agents.

In summary, this work demonstrates a new construction of 5-amino-oxazole-4-carboxylic esters that is amenable even

(14) (a) Nagata, W.; Yoshioka, M. *Tetrahedron Lett.* **1966**, *18*, 1913. (b) Nagata, W.; Yoshioka, M. *Org. React.* **1984**, *25*, 255.

Scheme 3. Preparation of Kinase Inhibitor **18**



to automated parallel synthesis. The end products are obtained in good yield and excellent purity. The new methodology is likely to be of value both in synthetic organic and medicinal chemistry research.

Acknowledgment. We thank the University of British Columbia, the Canada Research Chair Program, NSERC, CIHR, and MerckFrosst Canada for financial support. A portion of this work was carried out in France with financial support by Bayer CropScience, the MRT, and the CNRS ("BDI" Fellowship to P.Y.C.).

Supporting Information Available: Experimental procedures and characterization data for new compounds, plus NMR (^{1}H and ^{13}C) spectra of several products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101704R

(15) Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; Lowinger, T. B.; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775.