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Petasis Three-Component Coupling Reactions of Hydrazides for the Synthesis of Oxadiazolones and Oxazolidinones

Sebastian T. Le Quement,[†] Thomas Flagstad,[†] Remi J. T. Mikkelsen,[†] Mette R. Hansen,[†] Michael C. Givskov,[‡] and Thomas E. Nielsen*[,†]

Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark, and Department of International Health, Immunology and Microbiology, University of Copenhagen, DK-2200 Copenhagen, Denmark

ten@kemi.dtu.dk

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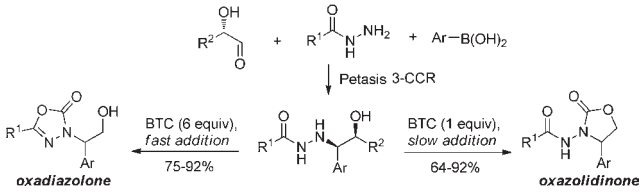
ABSTRACT



An application of readily available hydrazides in the Petasis 3-component coupling reaction is presented. An investigation of the substrate scope was performed to establish a general, synthetically useful protocol for the formation of hydrazido alcohols, which were selectively converted to oxazolidinone and oxadiazolone ring systems through triphosgene-mediated cyclization reactions.

Considering the huge potential of the three-component reaction of amines (primary or secondary), α-hydroxy aldehydes, and substituted vinyl or aryl boronic acids, also known as the Petasis three-component coupling reaction (Petasis 3-CCR),[1] for the stereoselective synthesis of amino alcohols,[2] there have been surprisingly few reports on its application in synthetic organic chemistry.[3] Evidence for the unique reliability of the reaction is illustrated by applications in the synthesis of natural products,[4] carbohydrate derivatives,[5] and unnatural amino acids.[6] Advantages of the reaction comprise simple and mild reaction conditions, broad substrate scope, easy access to building blocks, and amenability to combinatorial synthesis strategies, including those that aim for structurally diverse molecular libraries.[7]

As part of ongoing efforts aimed at identifying novel antibacterial compounds, we became interested in synthetic methods that allowed the rapid generation of compounds incorporating heterocyclic motifs analogous to those of renowned bioactives.

In this context, we have been particularly interested in the oxazolidinone core which is a key structural element of several known antibiotics, such as Linezolid[8] and *N*-thiolated 2-oxazolidinones.[9] This heterocycle could also serve

[†] Technical University of Denmark.
[‡] University of Copenhagen.

(1) For early accounts on the Petasis three-component coupling reaction, see: (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 586–583. (b) Harwood, L. M.; Currie, G. S.; Drew, M. G. B.; Luke, R. W. A. *Chem. Commun.* **1996**, 1953–1954. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 1700–1702.

(2) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799.

(3) For reviews on the Petasis three-component coupling reaction, see: (a) Petasis, N. A. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 199–223. (b) Batey, R. A. In *Boronic Acids*; Hall., D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 279–304. (c) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169–6193.

(4) For selected examples, see: (a) Batey, R. A.; MacKay, D. B. *Tetrahedron Lett.* **2000**, *41*, 9935–9938. (b) Jiang, B.; Xu, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2543–2546. (c) Sugiyama, S.; Arai, S.; Ishii, K. *Tetrahedron: Asymmetry* **2004**, *15*, 3149–3153. (d) Fürstner, A.; Ackerstaff, J. *Chem. Commun.* **2008**, 2870–2872.

(5) (a) Davis, A. S.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2004**, *69*, 3139–3143. (b) Hong, Z.; Liu, L.; Hsu, C.-C.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7417–7421.

(6) (a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446. (b) Currie, G. S.; Drew, M. G. B.; Harwood, L. M.; Hughes, D. J.; Luke, R. W. A.; Vickers, R. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2982–2990.

(7) (a) Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635–3638. (b) Muncipinto, G.; Kaya, T.; Wilson, J. A.; Kumagai, N.; Clemons, P. A.; Schreiber, S. L. *Org. Lett.* **2010**, *12*, 5230–5233. (d) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56.

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as a mimic of the lactone ring of *N*-acylated homoserine lactones which are signaling molecules involved in bacterial quorum sensing (Figure 1).[10]

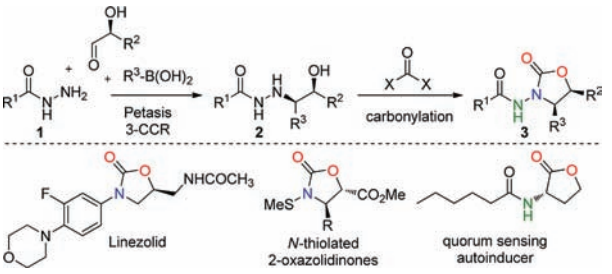
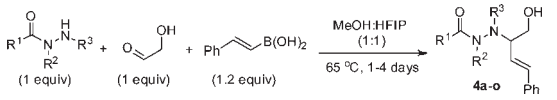


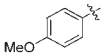
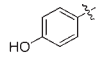
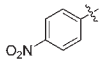
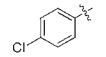
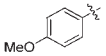
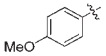
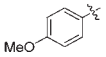
Figure 1. Synthetic strategy for the two-step generation of hydrazide-derived oxazolidinones (**3**).

To this end, it was envisioned that a Petasis 3-CCR of hydrazides **1** followed by subsequent carbonylative stitching of the resulting 1,2-hydrazido alcohol **2** would provide an expeditive entry toward such analogs (Figure 1, **3**). This strategy would also allow for systematic appendage variation of the hydrazide component, which may be functionalized at multiple positions before or after the Petasis 3-CCR, in the synthesis of combinatorial libraries.

Given their wide availability and synthetic utility, it is remarkable that hydrazides have not been reported as amine components in the Petasis 3-CCR. With a few reports on the use of structurally related carbazates (alkoxycarbonylated hydrazines) in mind,[11] we therefore set out to investigate this variant of the reaction. Several conditions (solvent, temperature, and stoichiometry) were thoroughly studied for the reaction of different hydrazides, glycolaldehyde, and *trans*-phenylvinylboronic acid by LC/MS, culminating in the use of a 1:1 mixture of MeOH and HFIP as solvent at 65 °C,[12] employing a slight excess of boronic acid (1.2 equiv) over the aldehyde and hydrazide components.[13] The developed protocol proved useful (Table 1), the desired products being obtained in yields ranging from 31 to 84%. Notably, *N*′-alkylated secondary hydrazides proved most efficient in the reaction

Table 1. Substrate Scope: Variation of the Hydrazide Component



entry	R^1	R^2	R^3	product, yield (%)[a, b]
1		H	H	**4a**, 52
2		H	H	**4b**, 63
3		H	H	**4c**, 56
4		H	H	**4d**, 49
5		H	H	**4e**, 80
6		H	H	**4f**, 64
7		H	H	**4g**, 0
8		H	H	**4h**, 37
9		H	H	**4i**, 31
10		H	H	**4j**, 53
11		H	H	**4k**, 74
12			H	**4l**, 0
13		H		**4m**, 64
14		H		**4n**, 71
15		H		**4o**, 84

[a] Isolated yield after flash column chromatography. [b] Reactions were generally run until conversion of starting hydrazide had stopped.

(entries 13−15). Unfortunately, products **4g** and **4l**, stemming from the reactions of 2-furoic hydrazide and *N*-allylbenzoylhydrazide, respectively, were not detected (entries 7 and 12). Variation of the boronic acid component clearly illustrates the reactivity profile of boronic acids in the Petasis 3-CCR (Table 2). Electron-rich 2-furylboronic acid proved to be highly reactive (**5g**, entry 7), whereas electron-neutral phenylboronic acid failed to react (**5h**, entry 8). Finally, the application of a range of aldehydes, previously reported for Petasis 3-CCRs, proved more difficult (entries 12−16). Gratifyingly, carbohydrate-derived **5m** was obtained in good yield (81%). Several attempts to apply glyoxal and salicylaldehyde all proved unfruitful (entries 15−16).

Following our original proposal, we then went on to subject the Petasis 3-CCR products to carbonylation conditions. Using known procedures,[14] we subjected Petasis

(8) (a) Müller, M.; Schimz, K.-L. *CMLS, Cell. Mol. Life Sci.* **1999**, *56*, 280–285. (b) Bozdogan, B.; Appelbaum, P. C. *Int. J. Antimicrob. Agents* **2004**, *23*, 113–119.

(9) Mishra, R. K.; Revell, K. D.; Coates, C. M.; Turos, E.; Dickey, S.; Lim, D. V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2081–2083.

(10) (a) Hentzer, M.; Eberl, L.; Nielsen, J.; Givskov, M. *Biodrugs* **2003**, *17*, 241–250. (b) Welch, M.; Mikkelsen, H.; Swatton, J. E.; Smith, D.; Thomas, G. L.; Glansdorp, F. G.; Spring., D. R. *Mol. BioSyst.* **2005**, *1*, 196–202. (c) Galloway, W. R. J. D.; Hodgkinson, J. T.; Bowden, S. D.; Welch, M.; Spring, D. R. *Chem. Rev.* **2011**, *111*, 28–67. (d) Mattmann, M. E.; Blackwell, H. E. *J. Org . Chem.* **2010**, *75*, 6737–6746.

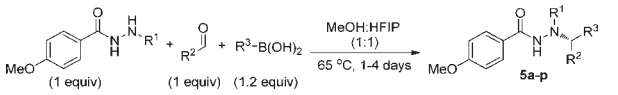
(11) (a) Portlock, D. E.; Naskar, D.; West, L.; Li, M. *Tetrahedron Lett.* **2002**, *43*, 6845–6847. (b) Portlock, D. E.; Osteszewski, R.; Naskar, D.; West, L. *Tetrahedron Lett.* **2003**, *44*, 603–605. (c) Neogi, S.; Roy, A.; Naskar, D. *J. Comb. Chem.* **2010**, *12*, 75–83. (d) Neogi, S.; Roy, A.; Naskar, D. *J. Comb. Chem.* **2010**, *12*, 617–629.

(12) Nanda, K. K.; Trotter, B. W. *Tetrahedron Lett.* **2005**, *46*, 2025–2028.

(13) See Supporting Information for a full account of the performed optimization experiments.

(14) (a) McReynolds, M. D.; Sportt, K. T.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 4673–4676. (b) Mishra, R. K.; Coates, C. M.; Revell, K. D.; Turos, E. *Org. Lett.* **2007**, *9*, 575–578.

Table 2. Substrate Scope: Variation of the Boronic Acid and Aldehyde Components



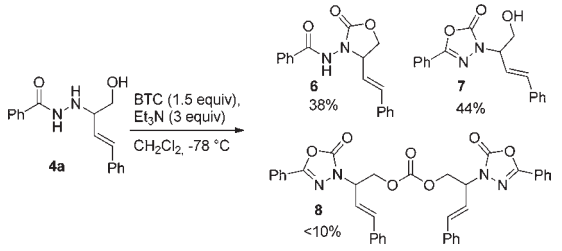
entry	R^1	R^2	R^3	product, yield (%)[a, b]
1	H	HO		**5a**, 26 (rac.)
2	H	HO		**5b**, 39 (rac.)
3	H	HO		**5c**, 48 (rac.)
4	H	HO		**5d**, 55 (rac.)
5	H	HO		**5e**, 64 (rac.)
6	H	HO		**5f**, 45 (rac.)
7	H	HO		**5g**, 95 (rac.)
8	H	HO		**5h**, 0
9	H	H		**5i**, 0[c]
10		H		**5j**, 75
11		H		**5k**, 51
12	H	HO, HO (rac.)		**5l**, 52 (rac.)
13	H	HO, HO, OH, OTBDMS		**5m**, 81
14	H	HO		**5n**, 77 (rac.)
15	H	OH		**5o**, 0[d]
16	H	O		**5p**, 0

[a] Isolated yield after flash column chromatography. [b] Reactions were generally run until conversion of starting hydrazide had stopped. [c] The product resulting from a double Petasis 3-CCR was isolated in 39% yield. [d] The intermediate imine was isolated in 49% yield.

3-CCR product **4a** to the one-pot addition of excess amounts of bis(trichloromethyl)carbonate (BTC), expecting clean conversion to the oxazolidinone product **6** (Scheme 1). LC/MS and TLC of the reaction showed not only instantaneous conversion of the starting material but also a complex reaction mixture containing several products. The two main products were isolated and assigned as the desired oxazolidin-2-one (oxazolidinone) **6** and the 1,3,4-oxadiazol-2-(3*H*)-one (oxadiazolone) **7**.

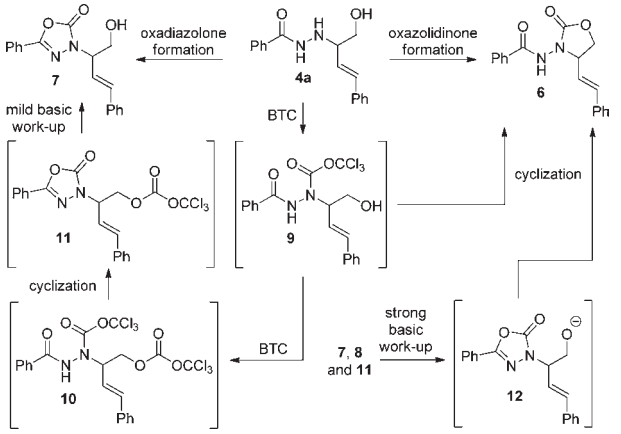
Intrigued by these findings, we decided to investigate if procedures could be developed for the selective synthesis of

Scheme 1. Reaction of Petasis 3-CCR Product **4a** with BTC



either of the two main products. We reasoned that formation of both products would proceed through common intermediate **9** (Scheme 2). Furthermore we speculated that oxadiazolone formation could be facilitated by the addition of excess amounts of BTC to the reaction mixture. This would lead to the formation of **10**, where the nucleophilic hydroxyl group was blocked, thereby enabling nucleophilic attack from the hydrazide carbonyl group to form the oxadiazolone product. These speculations were further supported by the isolation of trace amounts of carbonate dimer **8** (Scheme 1) which, probably, is formed through the intermediacy of **11** and nucleophilic attack by **7**. A mild basic workup of the reaction mixture then provided the oxadiazolone, by hydrolysis of **11** and any dimer **8** that was present. Contrarily, we found that the oxazolidinone **6** could be accessed via slow addition of stoichiometric amounts of BTC, where advantage was taken of the higher reactivity of the hydroxyl group.

Scheme 2. Proposed Pathway for the Generation of Oxazolidinone **6** and Oxadiazolone **7**



In accordance with the work of Milcent et al.,[15] we also speculated whether strong basic workup would convert any oxadiazolones present in the reaction mixture to the

(15) (a) Milcent, R.; Barbier, G.; Yver, B.; Mahzouz, F. *J. Heterocycl. Chem.* **1991**, *28*, 1511–1516. (b) Milcent, R.; Yver, B.; Barbier, G. *J. Heterocycl. Chem.* **1992**, *29*, 959–962. (c) Milcent, R.; Barbier, G. *J. Heterocycl. Chem.* **1992**, *29*, 1081–1084. (d) Milcent, R.; Yver, B.; Barbier, G. *J. Heterocycl. Chem.* **1993**, *30*, 905–908.

Scheme 3. Selective Conversion of Petasis 3-CCR Product via BTC-Mediated Carbonylation

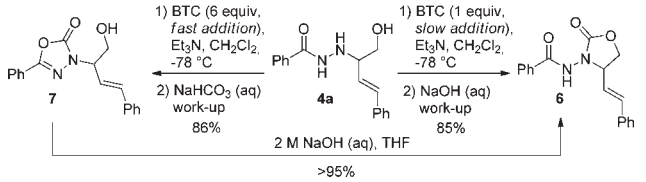
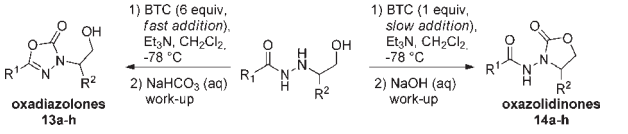
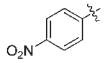
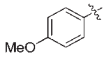
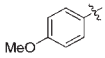
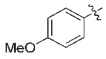


Table 3. BTC-Mediated Oxadiazolone and Oxazolidinone Formation



entry	R^1	R^2	oxadiazolone product, yield (%)[a,b]	oxazolidinone product, yield (%)[a,c]
1			**13a**, 85	**14a**, 65
2			**13b**, 81	**14b**, 92[d]
3			**13c**, 75	**14c**, 56[e]
4			**13d**, 86	**14d**, 92
5			**13e**, 87	**14e**, 84
6			**13f**, 88	**14f**, 88
7			**13g**, 75	**14g**, 0
8			**13h**, 76	**14h**, 74[e]

[a] Isolated yield after flash column chromatography. [b] No formation of oxazolidinone was observed. [c] Minor traces of oxadiazolone (~5%) were typically observed before aq. NaOH workup. [d] The oxadiazolone reaction mixture was added THF and 2 M NaOH (aq) to enable the *in situ* conversion of oxadiazolone to oxazolidinone. [e] The oxadiazolone reaction mixture was worked up, and the crude remaining oil was treated with THF and 2 M NaOH (aq).

desired oxazolidinone via *in situ* formation of oxy-anion **12**. Pleasingly, oxadiazolone **7** could be selectively synthesized by the fast addition of a large excess of BTC and a mild basic workup with sat. aqueous $NaHCO_3$ (Scheme 3). Oxazolidinone **6** was easily synthesized by the slow addition of 1 equiv of BTC and a strong basic workup (aqueous NaOH). In accordance with our considerations, subjecting oxadiazolone **7** to aqueous NaOH in THF provided oxazolidinone **6** in nearly quantitative yield.

We next synthesized two small libraries from structurally diverse Petasis 3-CCR products, which were selectively converted to either oxadiazolones or oxazolidinones via the developed reaction protocols (Table 3). In all instances, the desired oxadiazolones were easily accessed (yields between 75 and 88%). However, in a few cases, oxazolidinone formation was hampered by low solubility of the applied hydrazido alcohol (Table 3, entries 2, 3, and 8). For **14b**, this issue was circumvented by first forming the oxadiazolone with a large excess of BTC, followed by *in situ* conversion to the oxazolidinone using NaOH (aq). Similarly, **14c** and **14h** were obtained by conversion of the crude oxadiazolone to the oxazolidinone. We hypothesize that oxadiazolone formation is facilitated by the presence of intermediates similar to **11** (Scheme 2) which, generally, should display greatly enhanced solubilities in dichloromethane compared to the starting materials. Unfortunately, several workup strategies and the use of different reagent stoichiometries all failed to provide compound **14g**.

In summary, the use of hydrazides as amine components in the Petasis 3-CCR has been investigated. The reaction conditions were optimized, and the scope of the reaction with respect to hydrazides, boronic acids, and hydroxyaldehydes was examined. The resulting protocol allowed the routine preparation of synthetically versatile hydrazido alcohols, which were selectively converted into oxazolidinone and oxadiazolone ring systems via triphosgene-mediated cyclization processes. Ongoing work focuses on further diversification reactions of hydrazide-derived Petasis 3-CCR products for the creation of structurally diverse compound libraries for biological screening. All synthesized compounds are currently being tested for antibacterial activity, and results will be reported in due course.

Acknowledgment. The Technical University of Denmark, Danish Council for Independent Research (Natural Sciences), Danish Council for Strategic Research, Carlsberg Foundation, and Torkil Holm Foundation are gratefully acknowledged for financial support.

Supporting Information Available. Description of Petasis 3-CCR protocol optimization, experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.