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Sequential Multicomponent Reactions and a Cu-Mediated Rearrangement: Diastereoselective Synthesis of Tricyclic Ketones

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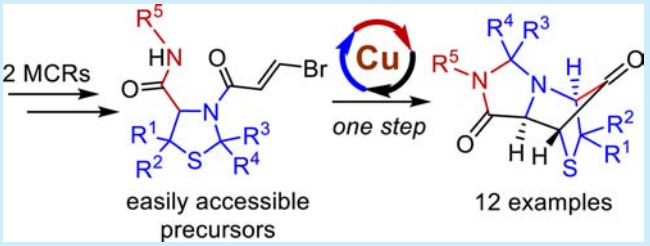
Supporting Information

ABSTRACT: A novel Cu-mediated rearrangement reaction based on bisamides containing a thiazolidine substructure opens the possibility for diastereoselective synthesis toward a tricyclic annulated and bridged heterocyclic system. The required precursors are easily synthesizable by a two-step synthetic pathway using the concept of sequential multicomponent reactions, i.e. the Asinger and Ugi reactions. Due to this synthesis strategy, a number of unique tricyclic heterocycles, characterized by high diversity, are synthesized in an effective manner.



Sulfur- and nitrogen-containing heterocycles such as imidazolidin-4-ones and thiomorpholines are remarkable pharmacophores in medicinal chemistry (Figure 1).[1−4]

In particular, the five-membered imidazolidin-4-one cycle can be found in natural products[5] as well as in a number of pharmaceuticals.[1−4] For example, it is part of the antibiotic prodrug hetacillin, which quickly metabolizes to the antibiotically active ampicillin.[1] It is applicable in the field of veterinary medicine.[2] Moreover, the imidazolidin-4-one core is a structural component of the antipsychotic fluspirilene, a drug used for the treatment of schizophrenia.[3] Furthermore, the six-membered thiomorpholine also indicates biological activity. As an example for the pharmacological relevance of this class of heterocycles, the matrix metalloprotease inhibitor prinomastat[4] can be pointed out.

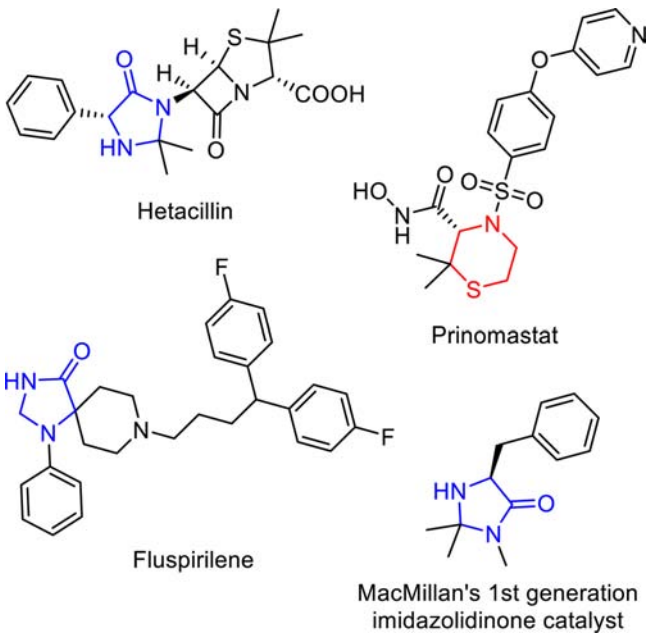


Figure 1. Representative imidazolidin-4-one- and thiomorpholine-containing compounds.

Besides the field of medicinal applications, the imidazolidin-4-ones are also well-known for their use as organocatalysts in synthetic organic chemistry. For example, MacMillan et al. reported that imidazolidinones are suitable catalysts for a wide variety of asymmetric reactions, such as enantioselective Diels−Alder or Friedel−Crafts alkylation reactions.[6]

Our group has a sustained interest in the synthesis of annulated heterocyclic systems.[7] Herein, we will present a diastereoselective Cu-mediated rearrangement reaction to annulated and bridged tricyclic systems, combining both the imidazolidin-4-one- and thiomorpholine-cycle. The precursors required for this rearrangement reaction are obtained from easily accessible substrates, such as aldehydes and ketones, in a two-step synthetic pathway using the modified Asinger four-component reaction (A-4CR)[8] and the Ugi three-component reaction (U-3CR)[9] (Scheme 1). This kind of reaction is now omnipresent in organic synthesis,[10] ranging from natural product synthesis[11] to combinatorial[12] or polymer chemistry,[13] and is a very helpful toolkit for the creation of multiple structural motifs of high diversity.

Based on the mentioned synthetic route, the first step suggests the use of A-4CR (Scheme 1). This reaction enables the efficient construction of five membered 2,5-dihydro-1,3-thiazoles (3-thiazolines) **1** based on an α-chloro aldehyde, a carbonyl compound (aldehyde or ketone), ammonia, and

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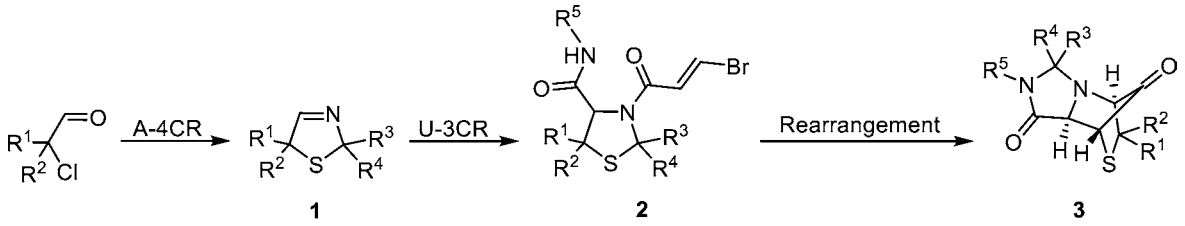
Scheme 1. Discovered Synthetic Pathway

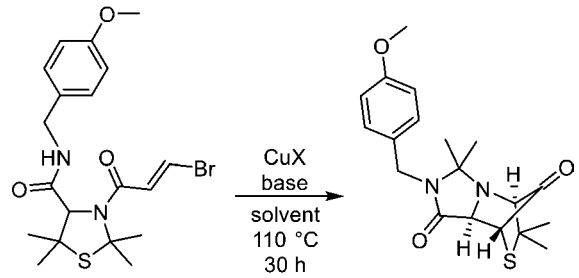


sodium hydrosulfide. By means of the modified A-4CR, six known 3-thiazolines were prepared in moderate yields of up to 73%.[14] The resulting heterocyclic structure **1** bears a reactive imine bond, which can be perfectly transformed into a bisamide structure including a thiazolidine backbone via the U-3CR.[9b] For this, the imines obtained are reacted with different isocyanides and *trans*-bromoacrylic acid (Scheme 1). The remaining substrates provide a necessary structural compartment in the resulting bisamides **2a–n** for the following reaction. However, using the U-3CR, all 3-thiazolines **1a–f** could be successfully converted into the corresponding bisamides **2a–n** in moderate-to-very-good yields of up to 88% (Table 2). Due to the utilization of different isocyanides, it is possible to implement benzylic, allylic, and aliphatic substituents at R^5 into the bisamidic scaffold **2**.

Initially, we focused on a Cu-catalyzed ring-closing reaction between the secondary amide and the brominated alkene carbon atom of the bisamides **2** under the formal elimination of hydrogen bromide. Following this strategy, we examined the conversion of **2a** using 10 mol % of CuI, 20 mol % of (*S*)-proline, and potassium carbonate (2 equiv) in DMF at 110 °C for 30 h. After column chromatography of the complex crude product mixture, one racemic diastereomer of the tricyclic ketone **3a** could be obtained in 7% yield. After some experiments under catalytic conditions, we found that an increase in the amount of copper compound also raised the yield of the tricyclic ketone **3a**. On the basis of these results, we started our investigation on the synthesis of the tricyclic ketone **3a** with bisamide **2a** (1 equiv) under variation of the copper compound (2 equiv), the base (5 equiv), and the solvent to establish optimal conditions (Table 1). At first, we examined the solvents DMF, DMSO, CH_3CN, and toluene (Table 1, entries 1–4). The formation of product **3a** was only observed using DMF. Thus, the following experiments were exclusively performed in DMF. Next, we examined the influence of the base. A decrease in the amount of base (3 equiv instead of 5 equiv) resulted in a lower yield of 20% in the case of K_2CO_3 (entry 5). Using Cs_2CO_3, the yield was similar to that reached with K_2CO_3 (entry 6). Et_3N did not lead to any product (entry 7). Referring to the work of Ernest[15a] and Ponsford,[15b] who described a $Cu(acac)_2$-mediated rearrangement reaction based on penicillins, we also tested Cu(II) compounds, such as the mentioned $Cu(acac)_2$ and $CuBr_2$ (entries 10 and 11). In the case of $CuBr_2$, the desired product could be isolated in 19% yield. Looking at Table 1, it is evident that CuI was the most effective copper compound for this rearrangement (entry 1). Further experiments showed that the combination of CuI with $CuBr_2$ in a 1:1 mixture is even more effective (entry 12). Therefore, the tricyclic ketone **3a** was obtained in 43% yield.

In order to explore the scope of the reaction, the rearrangement of bisamides **2a–n** was investigated under optimized conditions (Table 2).

Table 1. Reaction Optimization[a]



2a **3a**

entry	CuX	base	solvent	yield (%)[b]
1	CuI	K_2CO_3	DMF	31
2	CuI	K_2CO_3	DMSO	0
3	CuI	K_2CO_3	CH_3CN	0[c]
4	CuI	K_2CO_3	toluene	0
5	CuI	K_2CO_3	DMF	20[d]
6	CuI	Cs_2CO_3	DMF	33
7	CuI	Et_3N	DMF	0
8	CuBr	K_2CO_3	DMF	14
9	CuOAc	K_2CO_3	DMF	0
10	$Cu(acac)_2$	K_2CO_3	DMF	0
11	$CuBr_2$	K_2CO_3	DMF	19
12	CuI/$CuBr_2$ (1:1)	K_2CO_3	DMF	43

[a]All reactions were performed under an argon atmosphere using 0.5 mmol of **2a**, 1.0 mmol of CuX, 2.5 mmol of base in 10 mL of solvent, followed by column chromatography on silica gel. [b]Isolated yield after column chromatography. [c]The reaction was performed at 80 °C. [d]The reaction was performed using a reduced amount of base (1.5 mmol).

The results demonstrate that the performed rearrangement tolerates all of the tested substituents at position R^5. Thus, it was possible to prepare plenty of tricyclic ketones **3** with various R^5 substituents (benzylic, allylic, or aliphatic; Table 2, entries 1–12). Looking at Table 2, it becomes apparent that the substitution pattern of the 3-thiazoldine core (R^1–R^4) has a stronger influence than R^5 on the outcome of the rearrangement. The tetramethyl-substituted derivatives provide the products **3a–f** in a yield of up to 55% (entries 1–6). If the substituents R^3 and R^4 are modified to a spiro-connected six-membered system, the average yield decreased (entries 7 and 8). Comparison of the yields of the ketones **3d** (44% yield) and **3h** (34% yield) underlines this observation (entries 4 and 8). The utilization of two hydrogen substituents (entry 13) or one hydrogen and one phenyl substituent at R^3 and R^4 (entry 14) prevents a successful outcome. The conversion of the bisamides **2i–k** with a spiro-connection placed at substituents R^1 and R^2 leads to yields of up to 47% (entries 9–11). The rearrangement of the bisamide **2l** containing two spiro connections—both at position R^1 and R^2 as well as R^3 and R^4—to the corresponding tricyclic ketone **3l** afforded the highest yield of 61% (entry 12).

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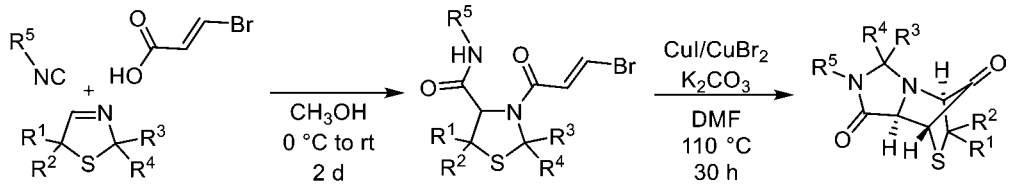
Table 2. Synthesis of Bisamides 2[a] and Tricyclic Ketones 3[b]



1 2 3

entry	imine	R^1	R^2	R^3	R^4	R^5	bisamide	yield (%)[c]	ketone[d]	yield (%)[c]
1	**1a**	CH_3	CH_3	CH_3	CH_3	$CH_2(4\text{-}OCH_3\text{-}C_6H_4)$	**2a**	44	**3a**	43
2	**1a**	CH_3	CH_3	CH_3	CH_3	$CH_2(4\text{-}CN\text{-}C_6H_4)$	**2b**	28	**3b**	40
3	**1a**	CH_3	CH_3	CH_3	CH_3	$(CH_2)_2C_6H_5$	**2c**	33	**3c**	52
4	**1a**	CH_3	CH_3	CH_3	CH_3	$CH_2CH{=}CH_2$	**2d**	58	**3d**	44
5	**1a**	CH_3	CH_3	CH_3	CH_3	$(CH_2)_3CH_3$	**2e**	61	**3e**	55
6	**1a**	CH_3	CH_3	CH_3	CH_3	*c*-C_6H_{11}	**2f**	72	**3f**	29
7	**1b**	CH_3	CH_3	$-(CH_2)_5-$		$CH_2(4\text{-}OCH_3\text{-}C_6H_4)$	**2g**	41	**3g**	30
8	**1b**	CH_3	CH_3	$-(CH_2)_5-$		$CH_2CH{=}CH_2$	**2h**	48	**3h**	34
9	**1c**	$-(CH_2)_5-$		CH_3	CH_3	$CH_2(4\text{-}OCH_3\text{-}C_6H_4)$	**2i**	66	**3i**	27
10	**1c**	$-(CH_2)_5-$		CH_3	CH_3	$CH(CH_3)_2$	**2j**	88	**3j**	25
11	**1c**	$-(CH_2)_5-$		CH_3	CH_3	$(CH_2)_3CH_3$	**2k**	73	**3k**	47
12	**1d**	$-(CH_2)_5-$		$-(CH_2)_5-$		$CH_2(4\text{-}OCH_3\text{-}C_6H_4)$	**2l**	33	**3l**	61
13	**1e**	CH_3	CH_3	H	H	$CH_2(4\text{-}OCH_3\text{-}C_6H_4)$	**2m**	65	**3m**	–
14	**1f**	CH_3	CH_3	H	Ph	*c*-C_6H_{11}	**2n**	41	**3n**	–

[a]The reaction was performed with imine **1** (1 equiv), *trans*-bromoacrylic acid (1 equiv), and isocyanide (1 equiv) in CH_3OH. [b]The reaction was performed under an argon atmosphere with bisamide **2** (1 equiv), CuI (1 equiv), $CuBr_2$ (1 equiv), and K_2CO_3 (5 equiv) in DMF. [c]Isolated yield after column chromatography. [d]Ketones **3** were obtained as single racemic diastereomer.

Thanks to the X-ray diffraction analysis of **3e**, the constitution of the unique tricyclic system could be confirmed (Figure 2). It is clear that the former thiazolidine scaffold and the *trans*-configured brominated acrylamide are no longer part of the resulting structure. In fact, one of the previous two amide groups is transformed into a ketone.

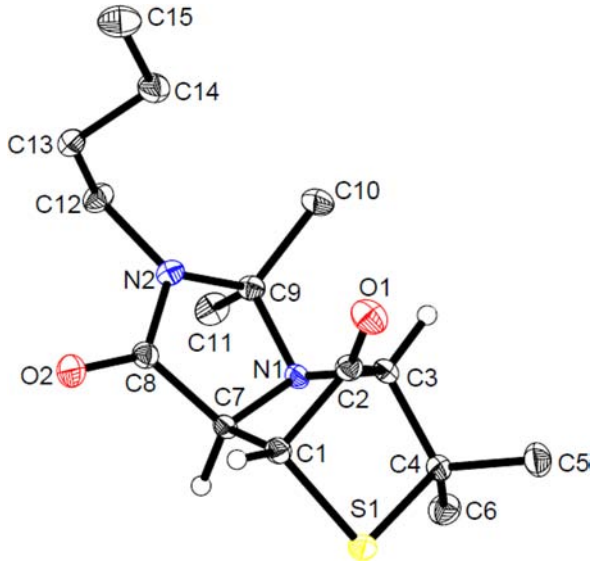


Figure 2. ORTEP drawing of the crystal structure of the tricyclic ketone **3e** (determined at 120 K); only one enantiomer is shown; displacement ellipsoids are shown with 50% probability.[16]

In conclusion, we have found and reported a diastereoselective Cu-mediated rearrangement for the first time. This reaction enables the conversion of bisamides containing a thiazolidine substructure toward an annulated and bridged tricyclic system consisting of an imidazolidin-4-one- and a thiomorpholine-cycle. Due to the fact that the deployed precursors result from the sequential combination of A-4CR and U-3CR, this strategy allows us to obtain the composition of a complex heterocyclic system with high diversity in a fast and simple manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03057.

Experimental procedures and compound characterization (PDF)

X-ray crystallographic data for compound **3e** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Sutherland, R.; Robinson, O. P. *Br. Med. J.* **1967**, *2*, 804. (b) Faine, S.; Harper, M. *Antimicrob. Agents Chemother.* **1973**, *3*, 15. (c) Jusko, W. J.; Lewis, G. P. *J. Pharm. Sci.* **1973**, *62*, 69.

(2) Office of the Federal Register National Archives and Records Administration *Code of Federal Regulations, Title 21, pt. 500−599: Food*

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Org. Lett. 2015, 17, 5866−5869

and Drugs, U.S. Government Printing Service: Washington, D.C., 2009; pp 167−169.
(3) (a) Janssen, P. A. J. PCT. Int. Appl. BE 633914 (A), 1963. (b) van Apen, J. H. *Psychiatr. Neurol. Neurochir.* **1970**, *73*, 277.
(4) Hande, K. R.; Collier, R.; Paradiso, L.; Stuart-Smith, J.; Dixon, M.; Clendeninn, N.; Yeun, G.; Alberti, D.; Binger, K.; Wilding, G. *Clin. Cancer Res.* **2004**, *10*, 909.
(5) (a) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Tetrahedron Lett.* **1977**, *18*, 61. (b) Djura, P.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 735. (c) Hu, J.-F.; Schetz, J. A.; Kelly, M.; Peng, J.-N.; Ang, K. K. H.; Flotow, H.; Leong, C. Y.; Ng, S. B.; Buss, A. D.; Wilkins, S. P.; Hamann, M. T. *J. Nat. Prod.* **2002**, *65*, 476. (d) Segraves, N. L.; Crews, P. *J. Nat. Prod.* **2005**, *68*, 1484. (e) Kochanowska, A. J.; Rao, K. V.; Childress, S.; El-Alfy, A.; Matsumoto, R. R.; Kelly, M.; Stewart, G. S.; Sufka, K. J.; Hamann, M. T. *J. Nat. Prod.* **2008**, *71*, 186. (f) Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 773. (g) Chang, R. S. L.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Albers-Schönberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. *Science* **1985**, *230*, 177. (h) Goetz, M. A.; Lopez, M.; Monaghan, R. L.; Chang, R. S. L.; Lotti, V. J.; Chen, T. B. *J. Antibiot.* **1985**, *38*, 1633. (i) Liesch, J. M.; Hensens, O. D.; Springer, J. P.; Chang, R. S. L.; Lotti, V. J. *J. Antibiot.* **1985**, *38*, 1638.
(6) (a) Ahrendt, K. A.; Borths, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.
(7) (a) Watzke, M.; Schulz, K.; Johannes, K.; Ullrich, P.; Martens, J. *Eur. J. Org. Chem.* **2008**, *2008*, 3859. (b) Johannes, K.; Martens, J. *Tetrahedron* **2010**, *66*, 242. (c) Stalling, T.; Saak, W.; Martens, J. *Eur. J. Org. Chem.* **2013**, *2013*, 8022. (d) Stalling, T.; Pauly, J.; Schmidtmann, M.; Martens, J. *Eur. J. Org. Chem.* **2014**, *2014*, 833. (e) Kröger, D.; Schlüter, T.; Fischer, M.; Geibel, I.; Martens, J. *ACS Comb. Sci.* **2015**, *17*, 202. (f) Kröger, D.; Brockmeyer, F.; Kahrs, C. *Org. Biomol. Chem.* **2015**, *13*, 7223.
(8) (a) Asinger, F. *Angew. Chem.* **1956**, *68*, 413. (b) Martens, J.; Offermanns, H.; Scherberich, P. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 668. (c) Drauz, K.; Koban, H. G.; Martens, J.; Schwarze, W. *Liebigs Ann. Chem.* **1985**, *1985*, 448. (d) Weber, M.; Jakobxht, J.; Martens, J. *Liebigs Ann. Chem.* **1992**, *1992*, 1.
(9) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Wischhöfer, E. *Chem. Ber.* **1962**, *95*, 136. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
(10) (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (b) Leon, F.; Rivera, D. G.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 1762. (c) Vercillo, O. E.; Kleber, Z.; Andrade, C.; Wessjohann, L. A. *Org. Lett.* **2008**, *10*, 205. (d) Vlaar, T.; Ruijter, E.; Znabet, A.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Orru, R. V. A. *Org. Lett.* **2011**, *13*, 6496. (e) Vlaar, T.; Mampuys, P.; Helliwell, M.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. *J. Org. Chem.* **2013**, *78*, 6735. (f) Huang, Y.; Khoury, K.; Chanas, T.; Dömling, A. *Org. Lett.* **2012**, *14*, 5916. (g) Zhao, T.; Boltjes, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2013**, *15*, 639. (h) Neochoritis, C. G.; Dömling, A. *Org. Biomol. Chem.* **2014**, *12*, 1649.
(11) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.
(12) Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem.* **2014**, *16*, 2958.
(13) Sehlinger, A.; Dannecker, P. K.; Kreye, O.; Meier, M. A. R. *Macromolecules* **2014**, *47*, 2774.
(14) (a) Stalling, T.; Brockmeyer, F.; Kröger, D.; Schwäblein, A.; Martens, J. *Z. Naturforsch., B: J. Chem. Sci.* **2012**, *67*, 1045. (b) Hatam, M.; Tehranfar, D.; Martens, J. *Synth. Commun.* **1995**, *25*, 1677. (c) Köpper, S.; Lindner, K.; Martens, J. *Tetrahedron* **1992**, *48*, 10277.
(15) (a) Ernest, I. *Tetrahedron* **1977**, *33*, 547. (b) Ponsford, R. J. *Tetrahedron Lett.* **1980**, *21*, 2451.
(16) CCDC-1432099 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.

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