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Furo- and thieno-fused 1,3-diazepine-4,6-diones

Merve Sinem Ozer [a], Gani Koza [a,b], Ertan Sahin [c], Metin Balci [a,*]

[a] Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey
[b] Department of Chemistry, Ahi Evran University, 40100 Kırşehir, Turkey
[c] Department of Chemistry, Atatürk University, 25240 Erzurum, Turkey

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ABSTRACT

We report the first preparation of furo- and thieno-fused 1,3-diazepine-4,6-dione derivatives starting from ethyl 2-(2-methoxy-2-oxoethyl)-3-furancarboxylate and -thiophencarboxylate. The ester functionalities connected to the hetero-ring were converted regiospecifically into the desired amides. The ester groups attached to the methylene unit were converted into isocyanates via Curtius rearrangement. The ring-closure reaction was performed in the presence of lithium bis(trimethylsilyl)amide at room temperature to give furo- and thieno-fused diazepinone derivatives.

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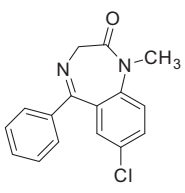
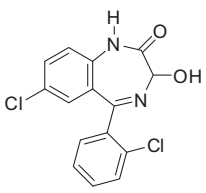
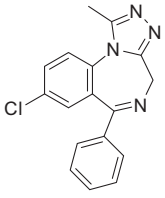
Benzodiazepinones represent one of the most prominent compound classes in terms of biological activity and pharmacological properties.[1] Among them, 1,4-benzodiazepine derivatives show a wide spectrum of biological activities[2] such as anxiolytic,[3] anticonvulsant,[4] antitumor,[5] and anti-HIV.[6] Also, they have been found to inhibit platelet aggregation behaving like the arginine–glycine–aspartic acid (RGD) peptide sequence,[7] and to disrupt the p53-Hdm2 protein–protein interaction inducing cell growth arrest and apoptosis.[8–10] Moreover, diazepam (**1**), commercially known as valium, is widely used in psychotherapy, and lorazepam (**2**) is a benzodiazepine drug showing all the characteristic pharmacological properties of this skeleton.[11]



Diazepam
1

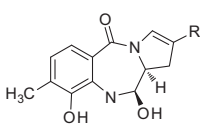


Lorazepam
2

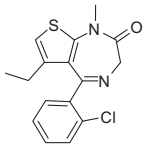


alprazolam
3

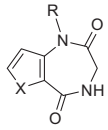
More importantly, the range of activity of these structures has been improved considerably through the fusion of the 1,4-benzodiazepine scaffold to a triazole ring.[12–14] Alprazolam (**3**) is used as an anxiolytic agent[15] and some other derivatives are employed as antidepressants.[16] The pyrrolobenzodiazepinone framework is encountered in a family of naturally occurring antitumor antibiotics, including anthramycin (**4**) and tilivalline; aptazepine with a pyrrolobenzodiazepine core is a novel antidepressant agent, which is undergoing clinical trials.[17]



R = alkyl or aryl anthramycin (R = CH=CHCONH$_2$)
4



clotiazepam
5



6a X = O
6b X = NH
R = 4-Cl-C$_6$H$_4$-CH$_2$-
4-CH$_3$O-C$_6$H$_4$-CH$_2$-

Various diazepinone derivatives in which the benzene ring is replaced by other heterocycles such as indole, pyrrole, pyridine, quinolone, etc., have been synthesized and their activities studied.[18] Thiophene is an isostere of the benzene ring. Clotiazepam (**5**),[19,20] which is a thiophene-fused diazepinone derivative,[21] is a marketed drug and possesses anxiolytic, sedative and muscle relaxant properties. On the other hand, furan-fused diazepinone derivatives are not common in the literature. de Meijere and coworkers[22] have described an approach to new types of pyrrolo- and furo-condensed perhydro[1,4]diazepine-2,5-diones **6** starting from spiro seven-membered ring compounds.

In this communication, we describe a synthetic methodology for the synthesis of 7,8-dihydro-4*H*-furo and thieno[2,3-*e*][1,3]diazepine-4,6(5*H*)-dione derivatives via Curtius rearrangement starting from the appropriate diesters attached to a heterocycle.

* Corresponding author. Tel.: +90 312 2105140; fax: +90 312 2103200.
E-mail address: mbalci@metu.edu.tr (M. Balci).

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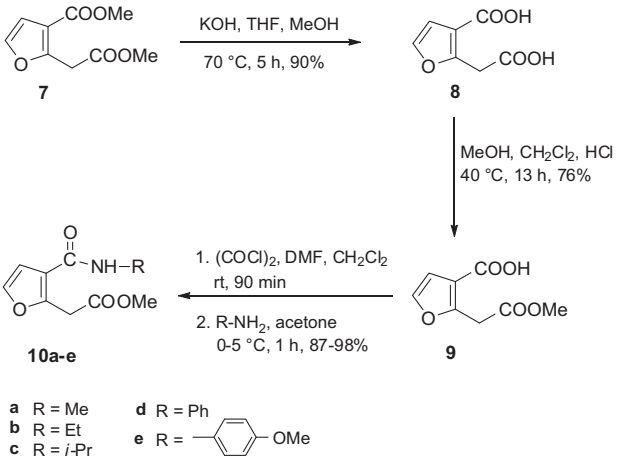
For the synthesis of furo-fused diazepinones, furo-amide derivatives **10a–e** were prepared from furan diester **7**, which was itself synthesized using the literature method.[23] Next, the ester groups in **7** were hydrolyzed to the corresponding dicarboxylic acid **8** with KOH at 70 °C. We previously reported that the reactivity of an ester group connected directly to an aromatic ring was lower than an ester connected to an alkyl group.[24] Therefore, an acid functionality adjacent to a furan ring is less reactive than a methylenic one. The non-conjugated acid functionality in **8** was converted regiospecifically into the corresponding monoester **9** in 76% yield by treatment of diacid **8** with concentrated HCl in methanol. Various amide derivatives **10a–e** were synthesized starting from monocarboxylic acid **9**. Thus, the monoacid **9** was firstly treated with oxalyl chloride to give the corresponding acyl chloride and subsequent treatment with alkyl- or aryl-substituted amines resulted in the formation of amides **10a–e** in high yields (Scheme 1).

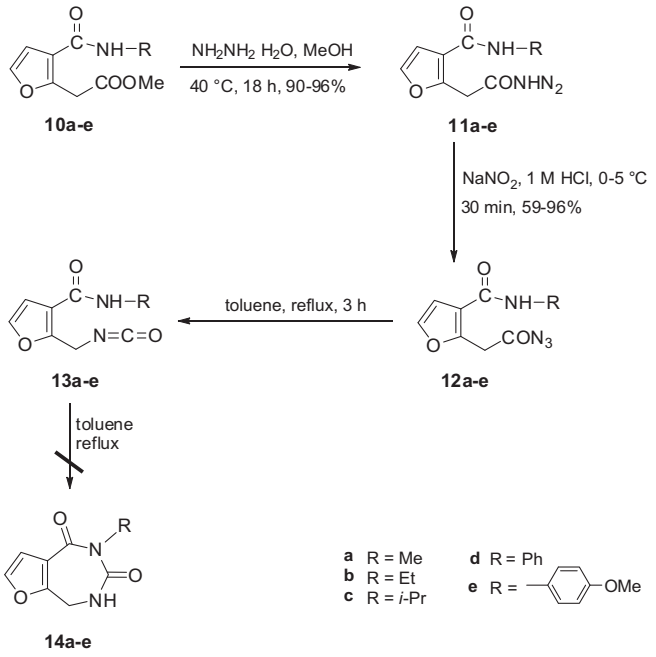
The construction of the desired heterocyclic ring systems **14** involved an intramolecular cyclization reaction of the isocyanate **13**, which can be generated by Curtius rearrangement.[25] The ester groups in **10a–e** were reacted with hydrazine monohydrate to give hydrazides **11a–e**. The resulting compounds were reacted with $NaNO_2$ and HCl at low temperatures to furnish the corresponding acyl azides **12a–e**. The acyl azide derivatives were heated at reflux temperature in toluene to give the key compounds, isocyanates **13a–e**, ready for cyclization (Scheme 2).

It was expected that the isocyanates **13a–e** would give the desired cyclization products **14a–e**. Unfortunately, all efforts, including increasing the temperature and prolonged reaction times failed to convert **13** into **14**. Therefore, we turned our attention to increasing the nucleophilicity of the nitrogen atom. We decided to use a base to deprotonate the amide proton to achieve this goal, and subjected amides **13a–c** to proton abstraction. Treatment with the non-nucleophilic strong base, lithium bis(trimethylsilyl)amide (LiHMDS) afforded the desired cyclization products **14a–c** in 52–83% yields (Scheme 3).

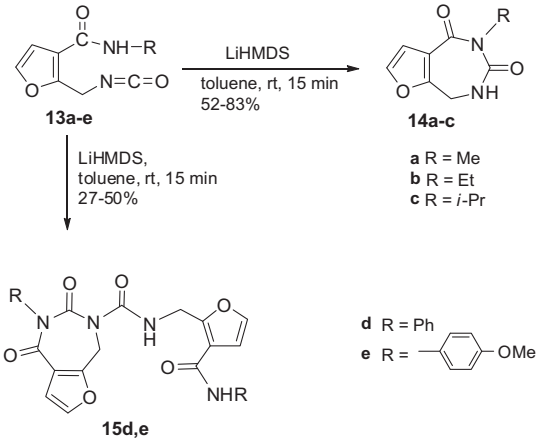
The NMR spectral data allowed the assignment of the structures. Additionally, X-ray diffraction analysis of a representative sample (**14c**) was carried out (Fig. 1).[26] The results confirmed unambiguously the desired structure. However, when the same reaction was carried out with the isocyanates **13d,e**, instead of the expected cyclization products, intermolecular condensation products **15d,e** were formed in lower yields (27% and 50%). When the R group attached to nitrogen was an alkyl group, the cyclization reaction proceeded smoothly. However, if the R substituent was an aryl group, the reaction did not stop at the intramolecular cyclization products, and the initially formed compounds



Scheme 1. Synthesis of furoamide derivatives **10a–e**.



Scheme 2. Synthesis of furo-isocyanate derivatives **13a–e**.



Scheme 3. Synthesis of furo-isocyanate derivatives **14a–c** and **15d,e**.

underwent further intermolecular reaction with the unreacted isocyanate **13d,e** to give the final products **15d,e**.

We propose that the cyclization products of type **14** have an acidic NH proton which is susceptible to abstraction under basic conditions. If R is an alkyl group, the anion formed after abstraction of the proton is not as stable as in the case of aromatic substituents, which contributes further to stabilization of these intermediates so that they can react with an additional equivalent of isocyanate to give the final products **15d,e**.

After successful construction of the furo-diazepinedione scaffold we turned our attention to the general applicability of this methodology to other heterocycles and synthesized two thieno-fused diazepinedione derivatives (**23a,b**) starting from the diester **16**. The starting material **16** was synthesized as described in the literature.[24c,27]

The ester groups of **16** were hydrolyzed to the corresponding dicarboxylic acid **17** with K_2CO_3 at reflux temperature in aqueous MeOH, and the non-conjugated acid functionalitiy was converted regiospecifically into the corresponding monoester **18** in 78% yield

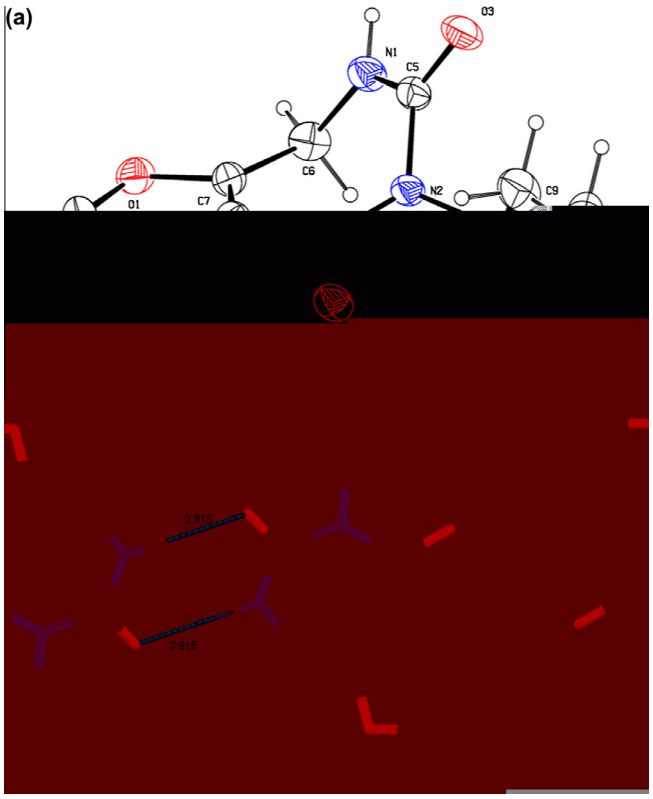
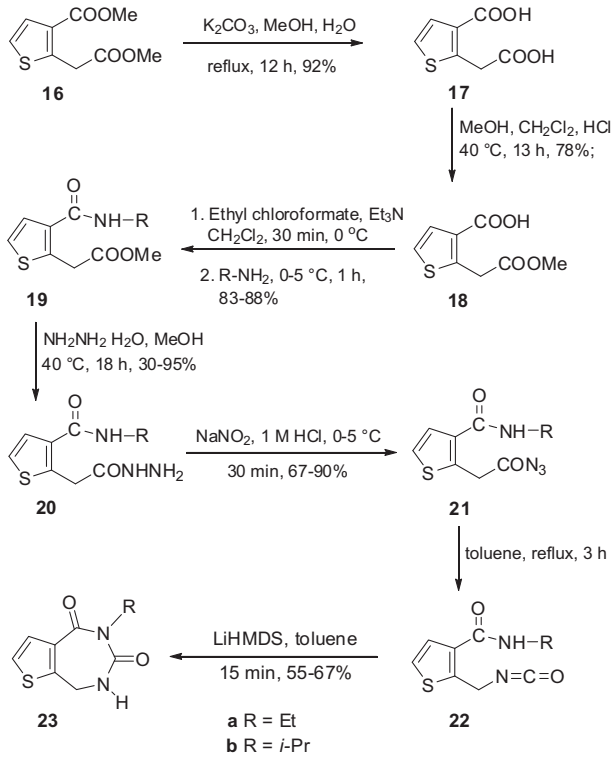


Figure 1. (a) ORTEP diagram of product **14c**. Thermal ellipsoids are shown at 50% probability level. (b) Dimeric structure with the *H*-bonding pattern (dashed lines) between the conformers.



Scheme 4. Synthesis of thienodiazepinedione derivatives **23**.

by treatment with concentrated HCl in methanol. Reaction of the monoacid with oxalyl chloride followed by subsequent reactions with amines failed to give the desired amides. Therefore, monoacids **18** were treated with ethyl chloroformate and triethylamine in CH_2Cl_2, followed by the amines. The corresponding amides **19** were formed in 83–88% yields (Scheme 4).

The ester groups in **19** were converted into acyl azides **21** as described above. The reactions of isocyanates **22** with LiHMDS furnished the desired thieno-fused diazepine-diones **23**.

In summary, we have achieved the synthesis of furo- and thieno-fused diazepinedione derivatives starting from heterocycles possessing adjacent ester groups. Formation of the diazepinedione skeleton was achieved in a single step by the addition of an in situ generated amide anion to the isocyanate functionality. To the best of our knowledge, this is the first report in which the construction of a diazepinedione unit was performed by addition of an anion to an isocyanate unit. Furthermore, we have shown the applicability of this synthetic method on two different systems: furan and thiophene. This methodology should also be applicable to other heterocycles for the generation of new diazapinedione-fused heterocycles.

Acknowledgements

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Supplementary data

Supplementary data associated (experimental conditions, spectroscopic data (^{1}H and ^{13}C NMR spectra), crystallographic information of compound **14c**) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.103.

References and notes

1. (a) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65–85; (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930; (c) Albright, J. D.; Feich, M. F.; Santos, E. G. D.; Dusza, J. P.; Sum, F. W.; Venkatesan, A. M.; Coupet, J.; Chan, P. S.; Ru, X.; Mazandarani, H.; Bailey, T. *J. Med. Chem.* **1998**, *41*, 2442–2444; (d) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132–143.
2. (a) Claremon, D. A.; Freidinger, R. M.; Liverton, N.; Selnick, H. G.; Smith, G. R. PCT Int. Appl. WO 9640656, **A1** 19961219, **1996**; *Chem. Abstr.* **1997**, *126*, 144295; (b) Herpin, T. F.; Van Kirk, K. G.; Salvino, J. M.; Yu, S. T.; Labaudiniere, R. F. *J. Comb. Chem.* **2000**, *2*, 513–521; (c) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235–2246.
3. Wright, W. B.; Brabander, H. J.; Greenbatt, E. N.; Day, I. P.; Hardy, R. A. *J. Med. Chem.* **1978**, *21*, 1087–1089.
4. (a) Weber, K.-H.; Bauer, A.; Danneberg, P.; Kuhn, F.-J. Ger. Offen. **1976**, DE 2445430, **A1** 19760401; *Chem. Abstr.* **1976**, *85*, 5699; (b) De Martino, G.; Massa, S.; Corelli, F.; Pantaleoni, G.; Fanini, D.; Palumbo, G. *Eur. J. Med. Chem.* **1983**, *18*, 347–350.
5. Thurston, D. E.; Bose, D. S.; Thompson, A. S.; Howard, P. W.; Leoni, A.; Croker, S. J.; Jenkins, T. C.; Neidle, S.; Hartley, J. A.; Hurley, L. H. *J. Org. Chem.* **1996**, *61*, 8141–8147.
6. Breslin, H. J.; Kukla, M. J.; Kromis, T.; Cullis, H.; De Knaep, F.; Pauwels, R.; Andries, K.; De Clercq, E.; Janssen, M. A. C.; Janssen, P. A. J. *Bioorg. Med. Chem.* **1999**, *7*, 2427–2436.
7. McDowell, R. S.; Gadek, T. R.; Barker, P. L.; Burdick, D. J.; Chan, K. S.; Quan, C. L.; Skelton, N.; Struble, M.; Thorsett, E. D.; Tischler, M.; Tom, J. Y. K.; Webb, T. R.; Burnier, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 5069–5076.
8. Marugan, J. J.; Leonard, K.; Raboisson, P.; Gushue, J. M.; Calvo, R.; Koblish, H. K.; Lattanze, J.; Zhao, S. Y.; Cummings, M. D.; Player, M. R.; Schubert, C.; Maroney, A. C.; Lu, T. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3115–3120.
9. Leonard, K.; Marugan, J. J.; Raboisson, P.; Calvo, R.; Gushue, J. M.; Koblish, H. K.; Lattanze, J.; Zhao, S. Y.; Cummings, M. D.; Player, M. R.; Maroney, A. C.; Lu, T. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3463–3468.
10. Leonard, K.; Marugan, J. J.; Koblish, H. K.; Calvo, R.; Raboisson, P.; Gushue, J. M.; Lattanze, J.; Zhao, S. Y.; Cummings, M. D.; Lu, T. B.; Player, M. R.; Maroney, A. *Clin. Cancer Res.* **2005**, *11*, 9152–9153.
11. Cox, C. E.; Reed, S. D.; Govert, J. A.; Rodgers, J. E.; Campbell–Bright, S.; Kress, J. P.; Carson, S. S. *Crit. Care Med.* **2008**, *36*, 706–714.
12. (a) Mohapatra, D. K.; Maity, P. K.; Shabab, M.; Khan, M. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241–5245; (b) Vachhani, D. D.; Kumar, A.; Modha, S. G.;

Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2013**, 1223–1227.
13. Vachhani, D. D.; Kumar, A.; Modha, S. G.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2013**, 1223–1227.
14. For a review on azole-fused benzodiazepines see: Gerecke, M.; Kyburz, E.; Borer, R.; Gassner, W. *Heterocycles* **1994**, *39*, 693–721.
15. Snyder, P. J.; Werth, J.; Giordani, B.; Caveney, A. F.; Feltner, D.; Maruff, P. *Hum. Psychopharm. Clin.* **2005**, *20*, 263–273.
16. (a) Greenblatt, D. J.; Harmatz, J. S.; Shapiro, L.; Engelhardt, N.; Gouthro, T. A.; Shader, T. A. *N. Engl. J. Med.* **1991**, *324*, 1691–1698; (b) Lahti, R. A.; Sethy, V. H.; Barsuhn, C.; Hester, J. B. *Neuropharmacology* **1983**, *22*, 1277–1282.
17. (a) Mostad, A.; Romming, C.; Storm, B. *Acta Chem. Scand. Ser. B* **1978**, *32*, 639–645; (b) Komatsu, N.; Kimura, K.; Abe, S.; Kagitani, Y. *J. Antibiot.* **1980**, *33*, 54–60; (c) Hurley, L. H. *J. Antibiot.* **1977**, *30*, 349–370; (d) Mori, S.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1986**, *27*, 6111–6114.
18. (a) Brouillette, Y.; Martinez, J.; Lisowski, V. *J. Org. Chem.* **2009**, *74*, 4975–4981; (b) Brouillette, Y.; Lisowski, V.; Fulcrand, P.; Martinez, J. *J. Org. Chem.* **2007**, *72*, 2662–2665. and references therein.
19. Mandrioli, R.; Mercolini, L.; Raggi, M. A. *Curr. Drug Metab.* **2008**, *9*, 827–844.
20. Nakanishi, M.; Tahara, T.; Araki, K.; Shiroki, M.; Tsumagari, T.; Takigawa, Y. *J. Med. Chem.* **1973**, *16*, 214–219.
21. (a) Kandeel, M. M.; Mounir, A. A.; Refaat, H. M.; Kassab, A. E. *J. Chem. Res.* **2012**, *36*, 105–110; (b) Huang, Y.; Domling, A. *Chem. Biol. Drug Des.* **2010**, *76*, 130–141; (c) Brouillette, Y.; Sujol, G.; Martinez, J.; Lisowski, V. *Synthesis* **2009**, 389–394; (d) Chimirri, A.; Gitto, R.; Grasso, S.; Romeo, G.; Zappala, M. *Heterocycles* **1992**, *34*, 1191–1200; (e) Fryer, R. I.; Earley, J. V.; Walser, A. *J. Heterocycl. Chem.* **1978**, *15*, 619–624.
22. Funke, C.; Es-Sayed, M.; de Meijere, A. *Org. Lett.* **2000**, *2*, 4249–4251.
23. Tada, M.; Ohtsu, K.; Chiba, K. *Chem. Pharm. Bull.* **1994**, *42*, 2167–2169.
24. (a) Koza, G.; Özcan, S.; Sahin, E.; Balci, M. *Tetrahedron* **2009**, *65*, 5973–5976; (b) Koza, G.; Karahan, E.; Balci, M. *Helv. Chim. Acta* **2010**, *93*, 1698–1704; (c) Koza, G.; Balci, M. *Tetrahedron* **2011**, *67*, 8679–8684; (d) Koza, G.; Keskin, S.; Özer, M. S.; Cengiz, B.; Şahin, E.; Balci, M. *Tetrahedron* **2013**, *69*, 395–409.
25. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.
26. Crystallographic data (excluding structure factors) of the structure **14c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 950126. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (Fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
27. Yun, S.; Kim, E.S.; Kim, H.S.; Ha, T.H.; Suh, K.-H.; Lee, G.S. From PCT Int. Appl. 2005, WO 2005087779, A1 20050922. *Chem. Abstr.* **2005**, *143*, 326345.