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Enols as Feasible Acid Components in the Ugi Condensation§

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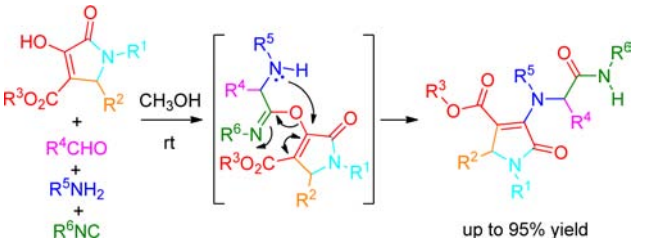
ABSTRACT



Heterocyclic enols are used for the first time as acid components in an Ugi-type multicomponent condensation. For that purpose, we have chosen enols containing a Michael acceptor, in order to facilitate an irreversible rearrangement of the primary Ugi adduct. The new four-component process leads readily and efficiently to heterocyclic enamines containing at least six elements of diversity.

Multicomponent reactions (MCR)[1] are highly convergent processes that lead to complex molecules with great efficiency and atom economy.[2] Particularly useful are MCR of isocyanides (IMCRs), as the Ugi four-component condensation (U4CC), in which carboxylic acids, carbonyl compounds, amines and isocyanides afford diversely functionalized α-acylamino amides.[3] Further structural diversity can be achieved through a wide variety of post-condensation transformations,[4] and we have successfully used this strategy for the synthesis of biologically relevant heterocycles,[5] β-dicarbonylic compounds,[6] amino acid derivatives[7] and retro-peptide building blocks.[8]

A conceivably even more powerful approach to scaffold diversity replaces one of the components by a new reagent that mimics its reactivity and chemical behavior.[9]

Significantly, the carboxylic acid is involved in several key steps of the classical U4CC, and hence its substitution leads to major structural changes.[1b,10] For example, the use

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§ Dedicated to the memory of our friend Stefano Marcaccini, who died October 1, 2012.

(1) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169. (c) Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115.

(2) Isambert, N.; Lavilla, R. *Chem.—Eur. J.* **2008**, *14*, 8444.

(3) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.

(4) Marcaccini, S.; Torroba, T. Post-Condensation Modifications of the Passerini and Ugi Reactions. In *Multicomponent Reactions*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005; p 33.

(5) (a) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1997**, *38*, 2519. (b) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Synthesis* **1997**, 1389. (c) Bossio, R.; Marcaccini, S.; Pepino, R.; Marcos, C. F. *J. Chem. Educ.* **2000**, *77*, 382. (d) Marcaccini, S.; Pepino, R.; Marcos, C. F.; Polo, C.; Torroba, T. *J. Heterocycl. Chem.* **2000**, *37*, 1501. (e) Marcos, C. F.; Marcaccini, S.; Pepino, R.; Polo, C.; Torroba, T. *Synthesis* **2003**, 691. (f) Neo, A. G.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 7977. (g) Marcos, C. F.; Marcaccini, S.; Menchi, G.; Pepino, R.; Torroba, T. *Tetrahedron Lett.* **2008**, *49*, 149. (h) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Heterocycles* **1997**, *45*, 1589. (i) Neo, A. G.; Carrillo, R. M.; Barriga, S.; Moman, E.; Marcaccini, S.; Marcos, C. F. *Synlett* **2007**, 327. (j) Marcaccini, S.; Neo, A. G.; Marcos, C. F. *J. Org. Chem.* **2009**, *74*, 6888.

(6) (a) Carrillo, R. M.; Neo, A. G.; Lopez-Garcia, L.; Marcaccini, S.; Marcos, C. F. *Green Chem.* **2006**, *8*, 787. (b) Neo, A. G.; Delgado, J.; Polo, C.; Marcaccini, S.; Marcos, C. F. *Tetrahedron Lett.* **2005**, *46*, 23.

(7) Faggi, C.; Neo, A. G.; Marcaccini, S.; Menchi, G.; Revuelta, J. *Tetrahedron Lett.* **2008**, *49*, 2099.

(8) Neo, A.; Carrillo, R.; Delgado, J.; Marcaccini, S.; Marcos, C. *Mol. Diversity* **2011**, *15*, 529.

(9) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.

(10) (a) Ugi, I.; Steinbruckner, C. *Angew. Chem., Int. Ed.* **1960**, *72*, 267. (b) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 2802. (c) Ugi, I. *Angew. Chem., Int. Ed.* **1962**, *1*, 9. (d) Rosendahl, K. H.; Ugi, I. *Liebigs Ann. Chem.* **1963**, 65. (e) Ugi, I.; Steinbruckner, C. *Chem. Ber. Recl.* **1961**, *94*, 734. (f) Heck, S.; Domling, A. *Synlett* **2000**, 424. (g) Bossio, R.; Marcaccini, S.; Pepino, R. *Liebigs Ann. Chem.* **1993**, 1229.

(11) Bossio, R.; Marcaccini, S.; Paoli, P.; Pepino, R.; Polo, C. *Synthesis* **1991**, 999.

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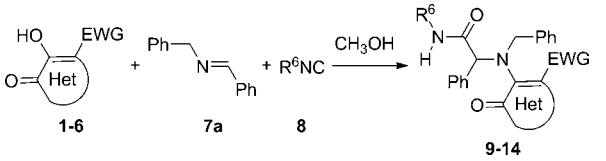
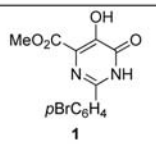
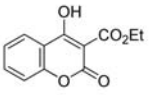
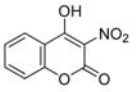
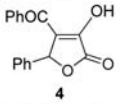
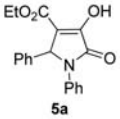
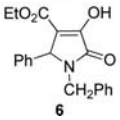
Table 1. Ugi Condensation with Heterocyclic Enols



entry	enol	reference	R^6	product[a,b] (% Yield)
1	 1	16a	cC_6H_{11}	**9** (70)
2	 2	16b	cC_6H_{11}	**10** (49)
3	 3	16c	*t*Bu	**11** (25)
4	 4	16d	cC_6H_{11}	**12** (70)
5	 5a	16e	cC_6H_{11}	**13a** (66)
6	 6		cC_6H_{11}	**14a** (28)

[a] General procedure: equimolar amounts of the reagents were stirred in methanol at rt for 72 h. [b] Yields are non optimized.

of phenols as acid surrogates was successfully introduced by Marcaccini,[11] and then applied by El Kaim to a series of reactions in which the primary adduct is stabilized through a Smiles rearrangement.[12] Enols have pK_a values comparable to that of phenols,[13] being sufficiently acidic to protonate imines. Furthermore, enolates are more nucleophilic than carboxylates, and thus able to trap the nitrilium intermediates formed in Ugi-type condensations. Surprisingly, with the only exception of a very recently published double Ugi reaction with highly acidic bis-enolic squaric acid,[14] the use of enols in such reactions is unprecedented.

We anticipate that the use of heterocyclic enol derivatives would provide a simple approach to the synthesis of libraries of compounds containing biologically privileged heterocyclic structures. As efficient IMCRs always include

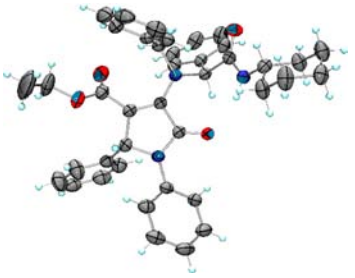
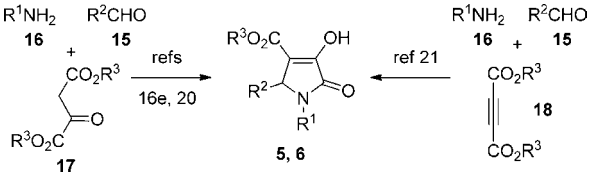


Figure 1. X-ray structure of Ugi adduct **13a**.

Scheme 1. Synthesis of Pyrrolidine-2,3-diones



an irreversible last reaction step,[3,12] we hypothesize that the viability of such processes would lie in the presence of specific structural motifs in the enol that make possible an irreversible transformation of the primary adduct. Here we demonstrate the viability of this novel alternative and its successful use for the straightforward synthesis of amino acid-derived heterocyclic enamines.[15]

Accordingly, we selected different 5- and 6-membered enolic heterocycles containing α,β-unsaturated electron-withdrawing groups (**1**–**6**).[16] Expectedly, they would react with Schiff bases and isocyanides to give Ugi-type primary adducts that would subsequently suffer a Michael-retro-Michael rearrangement to stable heterocyclic enamines (Table 1).

Thus, heterocyclic enols (**1**–**6**), (*E*)-*N*-benzylidene-1-phenylmethanamine (**7a**) and cyclohexyl or *terc*-butyl isocyanide (**8**; R^6 = c-C_6H_{11} or *t*-Bu) were mixed in methanol at rt. The reaction was followed by tlc, and the consumption of the starting enol and the formation of a new product was evident after a few hours. In all cases, the products were isolated in moderate or good yields and were successfully identified, according to their spectral data, as the expected Ugi-type adducts (**9**–**14**, Table 1). The structure of 3-amino-1*H*-pyrrol-2(5*H*)-one (**13a**; Table 1, entry 5), obtained as an almost equimolar mixture of the two possible

(12) (a) El Kaim, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7961. (b) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169. (c) Marcaccini, S.; Menchi, G.; Trabocchi, A. *Tetrahedron Lett.* **2011**, *52*, 2673.

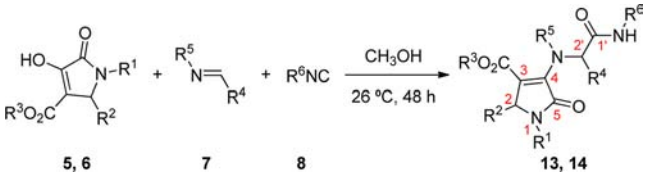
(13) Werstiuk, N. H.; Andrew, D. *Can. J. Chem.* **1990**, *68*, 1467.

(14) Aknin, K.; Gauriot, M.; Totobenazara, J.; Deguine, N.; Deprez-Poulain, R.; Deprez, B.; Charton, J. *Tetrahedron Lett.* **2012**, *53*, 458.

(15) Jourdan, F.; Kaiser, J. T.; Lowe, D. J. *Synth. Commun.* **2005**, *35*, 2453.

(16) (a) Zhong, Y.-L.; Zhou, H.; Gauthier, D. R., Jr.; Askin, D. *Tetrahedron Lett.* **2006**, *47*, 1315. (b) Stefanou, V.; Matiadis, D.; Melagraki, G.; Afantitis, A.; Athanasellis, G.; Igglessi-Markopoulou, O.; McKee, V.; Markopoulos, J. *Molecules* **2011**, *16*, 384. (c) Savel'ev, V. L.; Artamonova, O. S.; Troitskaya, V. S.; Vinokurov, V. G.; Zagorevskii, V. A. *Chem. Heterocycl. Compd.* **1973**, *9*, 816. (d) Gein, V.; Gein, L.; Bezmaternykh, É.; Voronina, E. *Pharm. Chem. J.* **2000**, *34*, 254. (e) Wasserman, H. H.; Koch, R. C. *J. Org. Chem.* **1962**, *27*, 35.

Table 2. Three-component Synthesis of 4-Aminoacil-pyrrolidones



entry	R^1	R^2	R^3	R^4	R^5	R^6	product[a] (% Yield)	diastereomeric ratio (A:B)
1	Ph	Ph	Et	Ph	$PhCH_2$	cC_6H_{11}	**13a** (95)	55:45[b]
2	Ph	Ph	Et	Ph	$PhCH_2$	*t*Bu	**13b** (92)	60:40
3	Ph	Ph	Et	Ph	$PhCH_2$	2,6-Me_2Ph	**13c** (81)	50:50
4	Ph	4-ClC_6H_4	Et	Ph	$PhCH_2$	cC_6H_{11}	**13d** (93)	60:40
5	Ph	4-ClC_6H_4	Et	Ph	$PhCH_2$	CH_2CO_2tBu	**13e** (72)	67:33
6	Ph	4-FC_6H_4	Et	Ph	$PhCH_2$	cC_6H_{11}	**13f** (88)	63:37
7	Ph	4-FC_6H_4	Et	Ph	$PhCH_2$	*t*Bu	**13g** (91)	50:50
8	Ph	4-FC_6H_4	Et	Ph	$PhCH_2$	2,6-Me_2Ph	**13h** (92)	55:45
9	Ph	4-FC_6H_4	Et	Ph	$PhCH_2$	CH_2CO_2tBu	**13i** (90)	50:50
10	Ph	4-$MeOC_6H_4$	Et	Ph	$PhCH_2$	$PhCH_2$	**13j** (84)	50:50
11	Ph	4-$MeOC_6H_4$	Et	Ph	$PhCH_2$	C_5H_{11}	**13k** (94)	50:50
12	Ph	3,4-$(OCH_2O)C_6H_3$	Et	Ph	$PhCH_2$	cC_6H_{11}	**13l** (94)	50:50
13	Ph	Ph	Et	Ph	3,4-$(OCH_2O)C_6H_3CH_2$	cC_6H_{11}	**13m** (84)	56:44
14	Ph	4-ClC_6H_4	Et	Ph	3,4-$(OCH_2O)C_6H_3CH_2$	*t*Bu	**13n** (80)	63:37
15	Ph	4-FC_6H_4	Et	Ph	3,4-$(OCH_2O)C_6H_3CH_2$	CH_2CO_2tBu	**13o** (83)	50:50
16	Ph	4-$MeOC_6H_4$	Et	Ph	3,4-$(OCH_2O)C_6H_3CH_2$	CH_2CO_2tBu	**13p** (88)	50:50
17	Ph	4-$MeOC_6H_4$	Et	Ph	3,4-$(OCH_2O)C_6H_3CH_2$	TOSMIC	**13q** (29)	60:40
18	Ph	3,4-$(OCH_2O)C_6H_3$	Et	Ph	3,4-$(OCH_2O)C_6H_3CH_2$	C_5H_{11}	**13r** (85)	55:45
19	Ph	4-$MeOC_6H_4$	Et	2-furil	$PhCH_2$	cC_6H_{11}	**13s** (68)	50:50
20	Ph	Ph	Et	2-furil	$PhCH_2$	*t*Bu	**13t** (66)	55:45
21	Ph	4-$MeOC_6H_4$	Me	Ph	$PhCH_2$	cC_6H_{11}	**13u** (86)	50:50
22	Ph	4-$MeOC_6H_4$	Me	Ph	3,4-$(OCH_2O)C_6H_3CH_2$	*t*Bu	**13v** (82)	64:36
23	$PhCH_2$	Ph	Et	Ph	$PhCH_2$	cC_6H_{11}	**14a** (70)	60:40
24	$PhCH_2$	Ph	Et	Ph	$PhCH_2$	*t*Bu	**14b** (67)	63:37

[a] For optimized reaction conditions, see Supporting Information. [b] *RS:RR* ratio.

diastereomers, was further confirmed by fractional crystallization and X-ray diffraction analysis of the *R,S* diastereomer (Figure 1).

To optimize the new reaction, we selected pyrrolidine-2,3-diones[17] with carboxyl substituents on position 4 (**5**, **6**; Scheme 1), which have drawn our attention as they are in the core of many natural products and drugs.[15,18] Importantly, the pyrrolidone scaffold have been demonstrated to be a privileged structure in the design of modulators of protein−protein interactions.[18,19] Advantageously, pyrrolidine-2,3-diones (**5**, **6**) are readily accessible through three-component reactions of aldehydes (**15**), amines (**16**) and, alternatively, alkyl oxalacetates (**17**),[16e,20] or acetylenedicarboxylates (**18**; Scheme 1),[21] which exponentially increases the diversity of products attainable from the Ugi-type condensation. Furthermore, the presence of a stereogenic center at position 5 of the ring could be advantageous, as it would lead to the formation of two readily separable diastereomeric products in the Ugi-type reaction.

After some optimization, successive addition of cyclohexyl isocyanide (**8**, R^6 = *c*-C_6H_{11}; 2 equiv) and the enol (**5a**, 1 equiv) to a solution of the imine (**7a**, 2 equiv) in methanol, and stirring the resulting mixture at 26 °C for 48 h afforded **13a** in 95% yield and a 55:45 *RS:RR* diastereomeric ratio.

To further explore the scope of this new condensation, we applied the optimized reaction conditions to different isocyanides (**8**), imines (**7**) and pyrrolidinodiones (**5**, **6**; Table 2). The reaction proceeds as expected, giving in all the cases the corresponding pyrrolidinonamines (**13**, **14**) in good to excellent yields. Remarkably, although the diastereomeric ratio was always close to 1:1, in many cases

(17) Vaughan, W. R.; Covey, I. S. *J. Am. Chem. Soc.* **1958**, *80*, 2197.

(18) (a) Thiel, P.; Kaiser, M.; Ottmann, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 2012. (b) Rose, R.; Erdmann, S.; Bovens, S.; Wolf, A.; Rose, M.; Hennig, S.; Waldmann, H.; Ottmann, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 4129. (c) Armisheva, M.; Kornienko, N.; Gein, V.; Vakhrin, M. *Russ. J. Gen. Chem.* **2011**, *81*, 1893.

(19) (a) Reddy, T. R. K.; Li, C.; Guo, X.; Myrvang, H. K.; Fischer, P. M.; Dekker, L. V. *J. Med. Chem.* **2011**, *54*, 2080. (b) Zhuang, C.; Miao, Z.; Zhu, L.; Dong, G.; Guo, Z.; Wang, S.; Zhang, Y.; Wu, Y.; Yao, J.; Sheng, C.; Zhang, W. *J. Med. Chem.* **2012**, *55* (22), 9630.

(20) Metten, B.; Kostermans, M.; Van Baelen, G.; Smet, M.; Dehaen, W. *Tetrahedron* **2006**, *62*, 6018.

(21) (a) Taylor, W.; Vadasz, A. *Aust. J. Chem.* **1982**, *35*, 1227. (b) Sun, J.; Wu, Q.; Xia, E.-Y.; Yan, C.-G. *Eur. J. Org. Chem.* **2011**, *2011*, 2981.

Scheme 2. Proposed Mechanism of the MCR with Enols

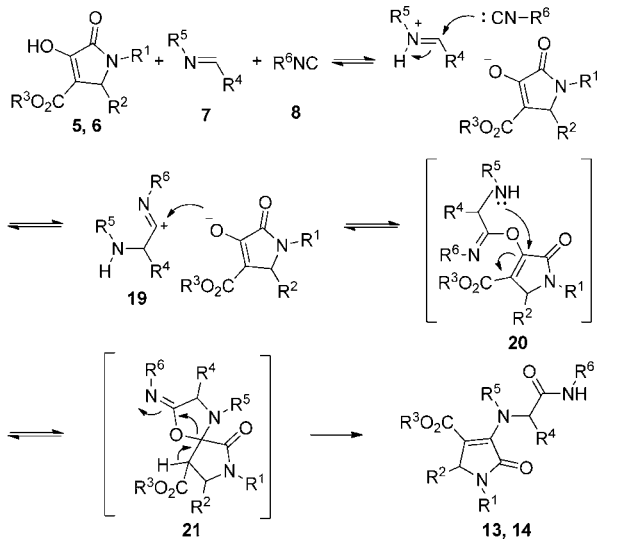
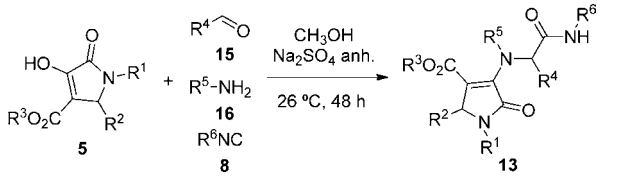


Table 3. Four-component Synthesis of 4-Aminoacil-pyrrolidones



entry	R^1	R^2	R^3	R^4	R^5	R^6	product (% yield)
1	Ph	Ph	Et	Ph	CH_2Ph	cC_6H_{11}	**13a** (86)
2	Ph	Ph	Et	Ph	CH_2Ph	*t*Bu	**13b** (85)
3	Ph	Ph	Et	Ph	3,4-(OCH_2O)-$PhCH_2$	cC_6H_{11}	**13m** (78)
4	Ph	4-MeOPh	Me	Ph	CH_2Ph	cC_6H_{11}	**13u** (90)

only one of the diastereoisomers spontaneously precipitates from the reaction mixture, and can be cleanly isolated by filtration. The NMR data suggest that the precipitate is always the *R,S* diastereoisomer, although an unequivocal assignation is not possible. Moreover, both diastereomers give distinctive spots on tlc and can be readily separated either by fractional crystallization or column chromatography.

In agreement with our initial hypothesis, the formation of pyrrolidinones **13** and **14** can be rationalized considering that the primary Ugi adducts **20** suffer an intramolecular conjugate addition of the amine nitrogen to the heterocyclic ring, followed by β-elimination of the imidate oxygen (Scheme 2). Similar intramolecular Michael addition–elimination processes have been observed in other systems,[22] but in the present case, this is especially favored, as an unstable imidate rearranges to a stable amide. This rearrangement plays a similar role to the usual *O* to *N* acyl migration in the classical U4CC, making the whole process irreversible and ensuring the efficiency of the reaction. As in the classic U4CC, the condensation with enols seems to be favored in polar solvents. However, surprisingly, it also takes place in toluene, although at a slower rate than in methanol.

We finally explored the possibility of performing the four-component condensation of isocyanides (**8**), enols (**5**), aldehydes (**15**) and amines (**16**), instead of using preformed imines (**7**). Consequently, benzaldehyde (**15**; R^4 = C_6H_5), benzylamine (**16**; R^5 = $CH_2C_6H_5$), cyclohexylisocyanide (**8**; R^6 = *c*-C_6H_{11}) and pyrrolidinodione (**5a**) were mixed in methanol in the usual reaction conditions. The expected aminopyrrolidine (**13a**) was isolated in a 70% yield, after 6 days. The reaction was then performed in the presence of anhydrous sodium sulfate to favor the formation of the imine. In this case, the yield was improved to 86% after only 48 h. Representative examples of this four-component condensation were also performed, and the expected products were obtained with good or excellent yields in all the cases (Table 3). Indeed, the operationally simpler four component condensation can be conveniently performed, with a minimal detriment on the yield.

In conclusion, we have developed a novel, efficient and high yielding IMCR in which, for the first time, heterocyclic enols are used as the acid partners in an Ugi type condensation. The reaction takes place smoothly at room temperature, with no need of catalysis. The success of this transformation lies in the structure of the enols that makes possible a conjugate addition-β-elimination rearrangement on the primary adduct. This approach constitutes a general, convenient and highly convergent synthesis of amino acid-derived enamines, which has been optimized for the preparation of biologically relevant 3-amino-1*H*-pyrrol-2(5*H*)-ones containing six elements of diversity. Further studies are underway to improve diastereoselectivities and to extend this new MCR to the synthesis of other heterocyclic and nonheterocyclic enamines.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds and the CIF of **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) (a) Okuda, K.; Watanabe, N.; Hirota, T.; Sasaki, K. *Tetrahedron Lett.* **2010**, *51*, 903. (b) Stiasni, N.; Kappe, C. O. *ARKIVOC* **2002**, 71.

The authors declare no competing financial interest.