Peculiarities of the tandem reaction between cyanoacetylenic alcohols and aminobenzoic acids: Synthesis of 5,5-dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles

Olesya A. Shemyakina, Anastasiya G. Mal'kina, Valentina V. Nosyreva, Igor' A. Ushakov, and Boris A. Trofimov*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Str., 664033, Irkutsk, Russia
E-mail: boris_trofimov@irioch.irk.ru

DOI: http://dx.doi.org/10.3998/ark.5550190.0013.827

Abstract

Tertiary cyanoacetylenic alcohols **1** reacting with 3-aminobenzoic acid (Et_3N, MeCN, 20–25 °C, 28–30 h) afforded 5,5-dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles **2** (77–85%). Under the same condition, 4-hydroxy-4-methylpent-2-ynenitrile **1a** and 2-aminobenzoic acid gave 2-[(5-iminio-2,2-dimethyl-2,5-dihydrofuran-3-yl)amino]benzoate **4** (39%). With 4-aminobenzoic acid, alcohol **1a** was almost quantitatively converted into the ester **5**.

Keywords: Aminobenzoic acids, cyanoacetylenic alcohols, 4,5-dihydrofurans, Knoevenagel condensation, nucleophilic addition, esterification

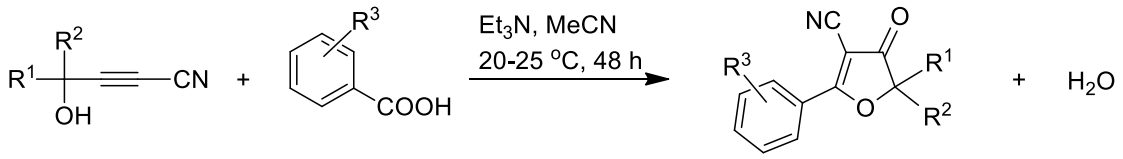
Introduction

4-Oxo-4,5-dihydrofurans occur widely in nature[1] and are interesting pharmacological objects exhibiting anticancer,[2] antiulcer,[3] antiallergic[4] and antifungal[5] properties. Some their functional derivatives find application as non-steroidal anti-inflammatory drugs and analgetics[6] as well as for the treatment of metabolic disorders.[7] Therefore, exploration of the chemistry and pharmacology of 4-oxo-4,5-dihydrofurans has progressed with vigor. Particular attention has been paid to the search for general and expedient syntheses of these important compounds and their controlled functionalization.[1f]

Recently, we have briefly reported a novel general methodology for the synthesis of 5,5-dialkyl-2-aryl-4-oxo-4,5-dihydrofuran-3-carbonitriles by the tandem reaction between cyanoacetylenic alcohols and substituted benzoic acids (Scheme 1).[8]

Despite the large suite of substituted benzoic acids applied to this reaction, aminobenzoic acids have not been used, because when these were treated with cyanoacetylenic alcohols,[9] the

reactions was shown to follow different courses. However, owing to the synthetic and pharmaceutical importance[10] of aminobenzoic acid derivatives (e.g., Novocain, Anaesthesin, Dicain, Novocainamide), additional effort to find conditions for the aminobenzoic acid-based synthesis of 3(2*H*)-furanones was felt justified. Here, we present the results of this research.

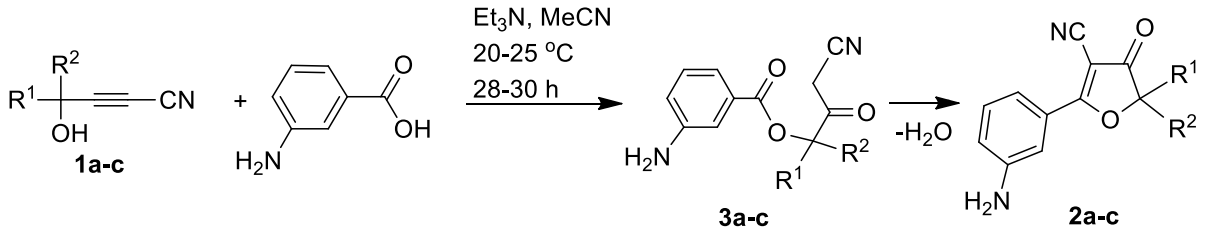


R^1, R^2 = alkyl, cycloalkyl; R^3 = H, 3-Me, 4-Me, 3-F, 2-Cl, 3-Cl, 2-Br, 3-I

Scheme 1

Results and Discussion

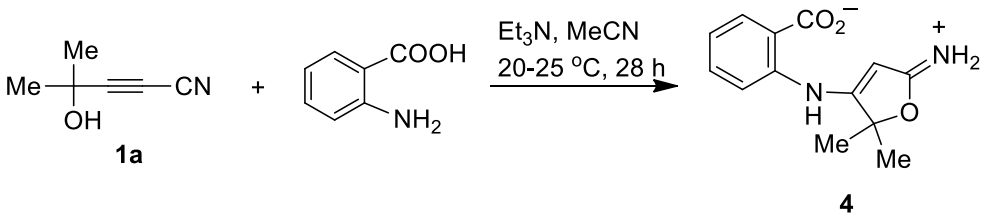
We found that 3-aminbenzoic acid reacting with cyanoacetylenic alcohols **1a–c** in the presence of an equimolar amount of Et_3N in MeCN at 20–25 °C does participate in the expected tandem sequence of reactions, leading to the formation of the desired 5,5-dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles **2a–c** in 77–85% yields (Scheme 2).



a: R^1, R^2 = Me; **b**: R^1 = Me, R^2 = Et; **c**: R^1-R^2 = $(CH_2)_5$

Scheme 2

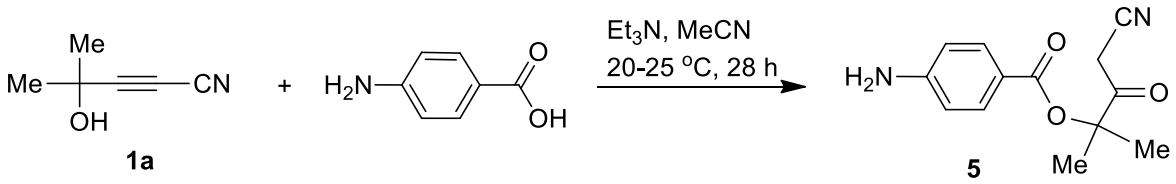
The formation of **2** is assumed[8] to proceed via the esters **3**, which subsequently undergo Knoevenagel condensation. Catalysis by Et_3N brings about cyclization, forming 4-oxo-4,5-dihydrofurans **2** instead of the esters **3** that have been previously observed.[9]



Scheme 3

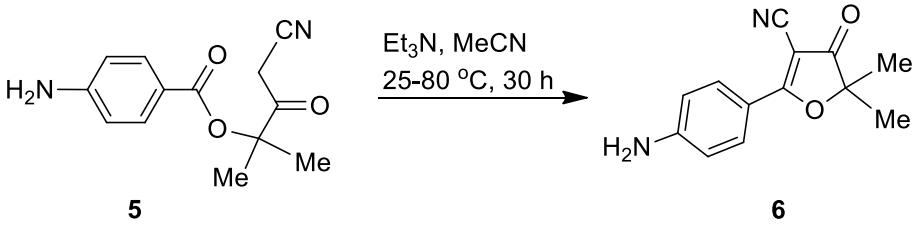
By contrast, 2-aminobenzoic acid, also in the presence of Et_3N, reacted with cyano–acetylenic alcohol **1a** in the same way as previously reported,[9] forming chemo- and region-selectively 2-[(5-iminio-2,2-dimethyl-2,5-dihydrofuran-3-yl)amino]benzoate (**4**) in 39% yield (74% without using the base catalyst) (Scheme 3).

Surprisingly, the reaction between 4-aminobenzoic acid and cyanoacetylenic alcohol **1a** led neither to the corresponding 4-oxo-4,5-dihydrofuran nor to 4-[(5-iminio-2,2-dimethyl-2,5-dihydrofuran-3-yl)amino]benzoate. In this case and under the above conditions (100 mol% Et_3N, MeCN, 20–25 °C, 28 h), the reaction stopped at the stage of ester **5** (96% yield) (Scheme 4).



Scheme 4

At a higher temperature (75–80 °C, other conditions being the same), ester **5** was partially converted into 2-(4-aminophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-carbonitrile **6**, (by ^1H NMR, GC-MS) in a mixture with the starting ester **5** (conversion 25%) (Scheme 5).



Scheme 5

Interestingly, under traditional Knoevenagel conditions (10 mol% piperidine, 20 mol% AcOH, benzene, 80 °C, 2 h[11] or 20 mol% β-alanine as catalyst, EtOH, 20–25 °C, 27 h[12]) as well as in the presence of KOH (20 mol%, EtOH, 20–25 °C, 24 h), the cyclization of ester **5** to 4-oxo-4,5-dihydrofuran **6** did not take place at all; the starting ester **5** was almost completely recovered.

The observed peculiarities of the reactivity of 2-, 3-, and 4-aminobenzoic acids toward cyanoacetylenic alcohols **1a–c** are likely to be due to differences in the steric and electronic interaction between amino and carboxylic groups. For 2-aminobenzoic acid, the initial esterification should be significantly sterically hindered compared to its 3- and 4-isomers. Besides, the intramolecular H-bonding between NH_2 and COOH groups may also slow down the ester formation. Consequently, this acid takes the alternative pathway of nucleophilic addition of the amino substituent to the triple bond.

The π-electron-donating effect of the amino substitutent toward the carboxylic group in 4-aminobenzoic acid is expected to decrease the electrophilicity of the carbonyl group, and hence hampers the Knoevenagel condensation with the CH_2CN moiety. This may explain the failure to form the 4-oxo-4,5-dihydrofuran derivative.

Conclusions

In summary, the tandem reactions of tertiary cyanoacetylenic alcohols **1a**–**c** with 2-, 3-, and 4-aminobenzoic acids (Et_3N, MeCN, 20–25 °C, 28–30 h) follow different courses, respectively: (i) nucleophilic addition of the amino group across the triple bond yielded 2-[(5-iminio-2,2-dimethyl-2,5-dihydro-3-furanyl)amino]benzenecarboxylate (**4**), (ii) cyclization forming 5,5-dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles (**2a–c**), (iii) formation of 4-cyano-2-methyl-3-oxobutan-2-yl 4-aminobenzoate (**5**). All products are prospective synthetic building blocks, potential drugs and/or rewarding precursors for their design.

Experimental Section

General. ^1H and ^{13}C NMR spectra of the products were recorded in $(CD_3)_2CO$ on a Bruker DPX-400 spectrometer (400.13 and 100.62 MHz, respectively). IR spectra of KBr pellets were measured on a Bruker Vertex-70 instrument. Mass spectra were recorded on an Agilent 5975C spectrometer. Sample introduction was carried out via an Agilent 6890N gas chromatograph: the column was an HP-5MS (0.25 mm × 30 m ×0.25 μm); carrier gas helium, constant flow. All melting points were taken on a Kofler micro hot stage. The reaction was monitored by TLC on neutral Al_2O_3 (chloroform/benzene/ethanol, 20:4:1 as eluent).

Aminobenzoic acids are commercial reagents (Merck). Cyanoacetylenic alcohols **1a–c** were prepared according to a published method.[13] Commercially available starting materials were used without further purification.

5,5-Dialkyl-2-(3-aminophenyl)-4-oxo-4,5-dihydrofuran-3-carbonitriles (2a–c). General procedure

To a solution of 3-aminobenzoic acid (0.137 g, 1.0 mmol) and Et_3N (0.101 g, 1.0 mmol) in MeCN (5 mL), the appropriate cyanoacetylenic alcohols **1a–c** (1.0 mmol) were added dropwise over 1 min. The reaction mixture was stirred at 20–25 °C for 28–30 h. The solvent was evaporated in vacuo, and the residue was purified by preparative TLC (SiO_2, $CHCl_3$/EtOAc, 1:1) to give products **2a**–**c**.

2-(3-Aminophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-carbonitrile (2a). Yellow powder (0.185 g, 81%); mp 186–188 °C. IR: ν_{max} 1214 (C-O-C), 1566, 1647 (C=C), 1707 (C=O), 2234 (CN), 3249 (C=CH), 3372, 3458 (NH_2) cm^{-1}. ^1H NMR (400.13 MHz, acetone-d_6): δ 1.53 (6H, s,

CH_3), 7.07 (1H, m, H-6), 7.34 (1H, m, H-5), 7.41 (1H, s, H-2), 7.45 (1H, m, H-4). ^{13}C NMR (100.61 MHz, acetone-d_6): δ 22.6 (CH_3), 87.7 (=C-CN), 91.1 [$(CH_3)_2$C], 113.1 (C-2), 113.3 (CN), 117.1 (C-6), 121.1 (C-4), 128.7 (C-1), 130.5 (C-5), 150.0 (H_2N-C), 187.4 (H_2N-C_6H_4-C=), 200.4 (C=O). MS: *m/z* (%) 228 (99) $[M]^+$, 143 (11), 142 (100), 120 (15), 115 (14), 114 (18), 92 (15), 65 (15). Anal. calc. for $C_{13}H_{12}N_2O_2$ (228.25): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.15; H, 5.39; N, 12.53.

2-(3-Aminophenyl)-5-ethyl-5-methyl-4-oxo-4,5-dihydrofuran-3-carbonitrile (**2b**). Yellow powder (0.186 g, 77%), mp 113–114 °C. IR: ν_{max} 1212 (C-O-C), 1589, 1632 (C=C), 1714 (C=O), 2225 (CN), 3233 (C=CH), 3372, 3460 (NH_2) cm^{-1}. ^{1}H NMR (400.13 MHz, acetone-d_6): δ 0.87 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 1.48 (3H, s, CH_3), 1.90 (2H, m, CH_2), 7.07 (1H, m, H-6), 7.33 (1H, m, H-5), 7.42 (1H, s, H-2), 7.43 (1H, m, H-4). ^{13}C NMR (100.61 MHz, acetone-d_6): δ 7.2 (CH_2CH_3), 20.9 (CH_3), 21.0 (CH_2), 88.7 (=C-CN), 93.8 (CH_3C), 113.1 (C-2), 113.3 (CN), 117.1 (C-6), 121.2 (C-4), 128.4 (C-1), 130.4 (C-5), 149.8 (H_2N-C), 188.0 (H_2N-C_6H_4-C=), 200.2 (C=O). MS: *m/z* (%) 242 (100) $[M]^+$, 227 (30), 214 (68), 142 (64), 120 (17), 115 (10), 114 (10), 92 (15), 65 (10). Anal. calcd for $C_{14}H_{14}N_2O_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.20; H, 6.03; N, 11.32.

2-(3-Aminophenyl)-4-oxo-1-oxaspiro[4.5]dec-2-ene-3-carbonitrile (**2c**). Yellow powder (0.229 g, 85%), mp 148–150 °C. IR: ν_{max} 1220 (C-O-C), 1589, 1606, 1628 (C=C), 1709 (C=O), 2223 (CN), 3240 (C=CH), 3374, 3457 (NH_2) cm^{-1}. ^{1}H NMR (400.13 MHz, acetone-d_6): δ 1.40-1.90 [10H, m, $(CH_2)_5$], 7.05 (1H, m, H-6), 7.33 (1H, m, H-5), 7.45 (1H, s, H-2), 7.46 (1H, m, H-4). ^{13}C NMR (100.61 MHz, acetone-d_6): δ 21.6, 24.6 and 31.8 [$(CH_2)_5$], 88.1 (=C-CN), 92.7 [$(CH_2)_5$C], 113.2 (C-2), 113.4 (CN), 117.1 (C-6), 121.1 (C-4), 128.7 (C-1), 130.4 (C-5), 149.9 (H_2N-C), 187.3 (H_2N-C_6H_4-C=), 200.0 (C=O). MS: *m/z* (%) 268 (96) $[M]^+$, 267 (14), 227 (16), 226 (32), 214 (14), 213 (100), 200 (11), 142 (41), 120 (25), 115 (19), 114 (10), 92 (39), 65 (12). Anal. calcd for $C_{16}H_{16}N_2O_2$ (268.32): C, 71.62; H, 6.01; N, 10.44. Found: C, 71.47; H, 6.16; N, 10.21.

2-[(5-Iminio-2,2-dimethyl-2,5-dihydrofuran-3-yl)amino]benzoate (4). To solution of 2-aminobenzoic acid (0.137 g, 1 mmol) and Et_3N (0.101 g, 1 mmol) in MeCN (5 mL), cyanoacetylenic alcohol **1a** (0.109 g, 1 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 20–25 °C for 28 h. The solvent was evaporated *in vacuo*, and the residue was washed with diethyl ether to give beige crystals **4** (0.096 g, 39%); mp 288–290 °C. IR, ^{1}H and ^{13}C NMR spectra correspond to literature data.[9]

4-Cyano-2-methyl-3-oxobutan-2-yl 4-aminobenzoate (5). To a solution of 4-aminobenzoic acid (0.137 g, 1 mmol) and Et_3N (0.101 g, 1 mmol) in MeCN (5 mL), cyanoacetylenic alcohol **1a** (0.109 g, 1 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 20–25 °C for 28 h. The solvent was evaporated *in vacuo*, and the residue was washed with diethyl ether to give yellow crystals of ester **5** (0.236 g, 96%); mp 157–158 °C. IR, ^{1}H and ^{13}C NMR spectra correspond to literature data.[9]

2-(4-Aminophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-carbonitrile (6). A solution of ester **5** (0.121 g, 0.5 mmol) and Et_3N (0.05 g, 0.05 mmol) in MeCN (2 mL) was stirred at 75-80

°C for 30 h. The solvent was removed and the residue was dried *in vacuo* to give a 3:1 mixture (^{1}H NMR and GC-MS) of ester **5** (0.121 g; 25% conversion) and 4-oxo-4,5-dihydrofuran-3-carbonitrile **6**, ^{1}H NMR (400.13 MHz, acetone-d_6): δ 1.46 (6H, s, CH_3), 6.83 and 8.00 (4H, m, *J* = 8.9 Hz, Ar). MS: *m/z* (%) 228 (32) $[M]^+$, 143 (11), 142 (100), 65 (12), 41 (12), 39 (16).

Acknowledgements

This work was supported by the President of the Russian Federation (program for the support of leading scientific schools, Grant No. NSh-3230.2010.3), the Russian Foundation for Basic Research (Grant No. 11-03-00203), Presidium of RAS (Program 25) and Integration Projects No. 93, 5.9.

References

1. (a) Martinelli, D.; Grossmann, G.; Séquin, U.; Brandl, H.; Bachofen, R. *BMC Microbiology* **2004**, *4*, 25. (b) Emura, M.; Yaguchi, Y.; Nakahashi, A.; Sugimoto, D.; Miura, N.; Monde, K. *J. Agric. Food Chem.* **2009**, *57*, 9909. (c) Dahlen, T.; Hauck, T.; Wein, M.; Schwab, W. *J. Biosci. Bioeng.* **2001**, *91*, 352. (d) Zabetakis, I.; Gramshaw, J. W.; Robinson, D. S. *Food Chem.* **1999**, *65*, 139. (e) Slaughter, J. C. *Biol. Rev.* **1999**, *74*, 259. (f) Haung, T. T.; Kirsch, S. F. In *Targets in Heterocyclic Systems-Chemistry and Properties*; Attanasi, O. A.; Spinelli, D. Eds.; Societa Chimica Italiana: Rome **2009**; Vol. 13, p 57.
2. (a) Ayral-Kaloustian, S.; Hollander, I.; Aulabaugh, A. US Patent 6710078 B2, 2004. (b) Crone, B.; Kirsch, S. F. *J. Org. Chem.* **2007**, *72*, 5435, and references therein. (c) Egi, M.; Azechi, K.; Saneto, M.; Shimizu, K.; Akai, S. *J. Org. Chem.* **2010**, *75*, 2123. (d) Rappai, J. P.; Raman, V.; Unnikrishnan, P. A.; Prathapan, S.; Thomas, S. K.; Paulose, C. S. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 764.
3. (a) Felman, S. W.; Jirkovsky, I.; Memoli, K. A.; Borella, L.; Wells, C.; Russell, J.; Ward, J. *J. Med. Chem*. **1992**, *35*, 1183. (b) Felman, S. W.; Jirkovsky, I. L.; Memoli, K. A. US Patent 5017601, 1991. (c) Felman, S. W.; Jirkovsky, I. L.; Memoli, K. A. US Patent 5389673, 1995.
4. (a) Mack, R. A.; Zazulak, W. I.; Radov, L. A.; Baer, J. E.; Stewart, J. D.; Elzer, P. H.; Kinsolving, C. R.; Georgiev, V. S. *J. Med. Chem.* **1988**, *31*, 1910. (b) Georgiev, V. S.; Kinsolving, C. R.; Mack, R. A. US Patent 4845122, 1989.
5. (a) Lee, J.-H.; Choi, I.-Y.; Kim, H.-J.; Choi, G.-J. US Patent 5889027, 1999. (b) Sung, W. S.; Jung, H. J.; Lee, I.-S.; Kim, H. S.; Lee, D. G. *J. Microbiol. Biotechnol.* **2006**, *16*, 349. (c) Sung, W. S; Jung, H. J.; Park, K.; Kim, H. S.; Lee, I.-S.; Lee, D. G. *Life Sciences* **2007**, *80*, 586.

6. (a) Silverstein, F. E.; Faich, G.; Goldstein, J. L.; Simon, L. S.; Pincus, T.; Whelton, A.; Makuch, R.; Eisen, G.; Agrawal, N. M.; Stenson, W. F.; Burr, A. M.; Zhao, W. W.; Kent, J. D.; Lefkowith, J. B.; Verburg, K. M.; Geis, G. S. *JAMA, J. Am. Med. Assoc.* **2000**, *284*, 1247. (b) Shin, S. S.; Byun, Y.; Lim, K. M.; Choi, J. K.; Lee, K.-W.; Moh, J. H.; Kim, J. K.; Jeong, Y. S.; Kim, J. Y.; Choi, Y. H.; Koh, H.-J.; Park, Y.-H.; Oh, Y. I.; Noh, M.-S.; Chung, S. *J. Med. Chem.* **2004**, *47*, 792. (c) Shamshina, J. L.; Snowden, T. S. *Tetrahedron Lett.* **2007**, *48*, 3767. (d) Shin, S. S.; Noh, M.-S.; Byun, Y. J.; Choi, J. K.; Kim, J. K.; Lim, K. M.; Kim, J. Y.; Choi, Y. H.; Ha, J.-Y.; Lee, K.-W.; Moh, J. H.; Jeong, Y. S.; Chung, S.; Joo, Y. H.; Lee, C. H.; Kang, S. H.; Park, Y.-H.; Yi, J. B. Patent WO/2000/061571, 2000.
7. Jung, J.-K.; Semple, G.; Johnson, B. R. US Patent 7803837 B2, 2010.
8. Trofimov, B. A.; Shemyakina, O. A.; Mal'kina, A. G.; Ushakov, I. A.; Kazheva, O. N.; Alexandrov, G. G.; Dyachenko, O. A. *Org. Lett*. **2010**, *12*, 3200.
9. Trofimov, B. A.; Mal'kina, A. G.; Shemyakina, O. A.; Nosyreva, V. V.; Borisova, A. P.; Albanov, A. I.; Kazheva, O. N.; Alexandrov, G. G.; Chekhlov, A. N.; Dyachenko, O. A. *Tetrahedron* **2009**, *65*, 2472.
10. (a) Mashkovskii, M. D. *Lekarstvennye sredstva (Drugs)*; Novaya Volna: Moscow, 2003 (in Russian). (b) Madrakian, T.; Afkhami, A.; Khalafi, L.; Mohammadnejad, M. *J. Braz. Chem. Soc.* **2006**, *17*, 1259. (c) Lehmann, T.; Albers, M.; Rölle, T.; Müller, G.; Hebler, G.; Tajimi, M.; Ziegelbauer, K.; Okigami, H. Patent PCT Int. Appl.WO 03/030889 A1, 2003. (d) Abd El Wahed, M. G.; Abd El Wanees, S.; El Gamel, M.; Abd El Haleem, S. *J. Serb. Chem. Soc.* **2004**, *69*, 255. (e) Varnavas, A.; Lassiani, L.; Valenta, V.; Mennuni, L.; Makovec, F.; Hadjipavlou-Litina, D. *Eur. J. Med. Chem.* **2005**, *40*, 563. (f) Correa-Basurto, J.; Alcántara, I. V.; Espinoza-Fonseca, L. M.; Trujillo-Ferrara, J. G. *Eur. J. Med. Chem.* **2005**, *40*, 732. (g) Shen, H. C.; Ding, F.-X.; Luell, S.; Forrest, M. J.; Carbollo-Jane, E.; Wu, K. K.; Wu, T.-J.; Cheng, K.; Wilsie, L. C.; Krsmanovic, M. L.; Taggart, A. K.; Ren, N.; Cai, T.-Q.; Deng, Q.; Chen, Q.; Wang, J.; Wolff, M. S.; Tonq, X.; Holt, T. G.; Waters, M. G.; Hammond, M. L.; Tata, J. R.; Colleti, S. L. *J. Med. Chem.* **2007**, *50*, 6303.
11. *Organikum, Organisch-Chemisches Grundpraktikum*, 21st Edn.; Wiley-VCH: Weinheim **1998**, p 527f.
12. Amancha, P. K.; Lai, Y.-C.; Chen, I.-C.; Liu, H.-J.; Zhu, J.-L. *Tetrahedron* **2010**, *66*, 871.
13. (a) Landor, S. R.; Demetriou, B.; Grzeskowiak, R.; Pavey, D. *J. Organomet. Chem.* **1975**, *93*, 129. (b) Trofimov, B. A.; Andriyankova, L. V.; Shaikhudinova, S. I.; Kazantseva, T. I.; Mal'kina, A. G.; Afonin, A. V. *Synthesis* **2002**, 853.

