HETEROCYCLES, Vol. 68, No. 7, 2006, pp. 1443 – 1449. © The Japan Institute of Heterocyclic Chemistry
Received, 31st March, 2006, Accepted, 11th May, 2006, Published online, 12th May, 2006. COM-06-10753

POLYPHOSPHORIC ACID-INDUCED CONSTRUCTION OF QUINAZOLINONE SKELETON FROM 1-(3,4-DIMETHOXYPHENYL)-3-PHENYLUREA AND CARBOXYLIC ACIDS

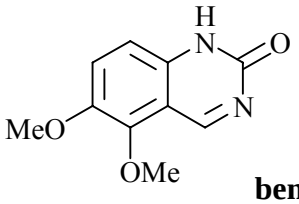
Iliyan Ivanov*, Stoyanka Nikolova, Ekaterina Kochovska, and Stela Statkova-Abeghe

University of Plovdiv, Department of Organic Chemistry, 4000 Plovdiv, Bulgaria

Abstract – A general synthesis of a series 4-substituted 3,4-dihydro-2(1*H*)-quinazolinones (**7**) included polyphosphoric acid (PPA)-induced cyclization with carboxylic acids. Modification at the 4-position of the quinazolinone skeleton was best achieved by variation of carboxylic acids. Starting 1-(3,4-dimethoxyphenyl)-3-phenylurea (**3**) was prepared from the phenylisocyanate and 3,4-dimethoxyaniline.

INTRODUCTION

Substituted ureas have been of great interest due to appearance of this functionality in drug candidates such as HIV protease inhibitors,[1] FKBP12 inhibitors,[2] CCK-B receptor antagonists[3] and endothelin antagonists.[4] These ureas were used for starting agents in the synthesis of N^3-substituted 2(1*H*)-quinazolinones.[5] The quinazoline skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances capable of exhibiting a wide variety of biological activities. Many of quinazolinone alkaloids such as tryptanthrine, vasicinone, anisotine and rutaecarpine[6] demonstrate important biological activities. A series of 2(1*H*)-quinazolinones were investigated, as compounds with cardiotonic activity. The most active analogue of them was 5,6-dimethoxy-4-methyl-2(1*H*)-quinazolinone (ORF 16600, bemarinone).



bemarinone

Bemarinone is about twice the intravenous potency of other drugs for parenteral use, as orally potent agents. These agents acted through selective inhibition of cardiac fraction III cyclic nucleosidephosphodiesterase (PDE-III).[5,7] Some quinazolinone derivatives are potent, selective, and structurally new inhibitors of the Fe(II) enzyme *Escherichia coli* peptide deformylase (PDF).[8] The quinazolinones, as intermediates in the synthesis of triazolobenzodiazepine derivatives,[9] were investigated in several research laboratories, as potent antagonists of platelet activating factor (PAF), because of their selectivity, potency and bioavailability. Besides, 2-methyl-4(3*H*)-quinazolinones carrying alkyl, cycloalkyl, aralkyl or aryl substituents at N-3 of the quinazolinone ring exhibit analgetic, antipyretic and antiinflamatory activities comparable to those of aspirin and phenylbutazone.[10] The quinazolinone compounds are useful as alpha-1-adrenergic receptor antagonists.[11] They also are agonists on human ORL1 (nociceptin) receptor.[12]

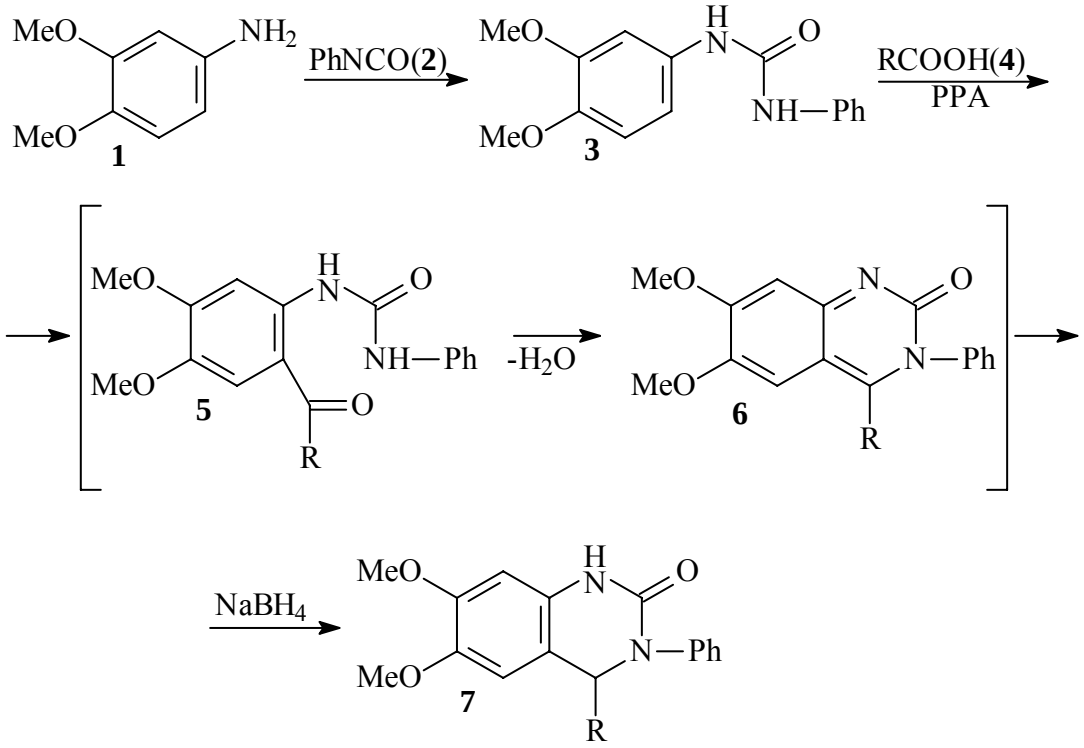
RESULTS AND DISCUSSION

In view of these observations, we had to synthesize different quinazolinones, as compounds with expected biological activity.

Some authors obtained quinazolinones from iodoquinazolinones prepared by boiling aminobenzophenone with urea in acetic acid. The iodoquinazolinone was converted to acetylhydrazine by reacting in first with potassium *tert*-butoxide and diethyl chlorophosphate to form the intermediate 2-(phosphoryloxy)quinazoline and then treating it *in situ* with acetylhydrazine. Ring closure to final product by dehydration was effected by heating in PPA up to 190°C.[9] Other methods starts with monoalkylation of 2-aminobenzylamines with ethyl bromoacetate in dioxane at reflux. Ring closure was achieved with either bis(trichloromethyl) carbonate in dioxane.[8] Recently, Vicente *et al.* reported the first ortho-palladated arylurea complexes, obtained by oxidative addition reactions, and have studied their reactivity toward different reagents to prepare quinazolinone derivatives.[13] The Friedel-Crafts acylation of activated benzene rings in the presence of polyphosphoric acid is a very convenient method for direct synthesis of aromatic ketones.[14] In our previous reports, we have shown that the reaction of 2-(3,4-dimethoxyphenyl)ethylamine with carboxylic acids, their esters or anhydrides in PPA affords the corresponding 3,4-dihydroisoquinolines in very good yields and purity.[15] This reaction was also applied to preparation of 1-substituted 3,4-dihydro-β-carbolines.[16]

In this paper we describe PPA-induced construction of 3,4-disubstituted quinazolinone skeleton by acylation of 1-(3,4-dimethoxyphenyl)-3-phenylurea with different carboxylic acids. Starting urea **3** was obtained from the 3,4-dimethoxyaniline (**1**) and phenylisocyanate (**2**). We found that the reaction of 1-(3,4-dimethoxyphenyl)-3-phenylurea (**3**) with acetic acid (**4a**) in PPA at 80°C for 6 h afforded the 4-methyl-6,7-dimethoxy-3-phenyl-2(3*H*)-quinazolinone (**6a**). We assume that in this reaction acylation of

the benzene ring takes place first to afford an intermediate (**5a**), which spontaneously cyclized to **6a**. 6,7-Dimethoxy-4-methyl-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (**7a**) was easily obtained by treatment of **6a** with $NaBH_4$ in methanol in moderate yield. These results prompted us to continue our research to prepare different quinazolinones. By analogy we obtained derivatives (**7b-i**), as products of different carboxylic acids (**4b-i**) (Scheme 1 and Table 1).



Scheme 1

Table 1. Reaction of 1 and RCO_2H

Entry	R	Yield, [%]
7a	CH_3	55
7b	C_2H_5	52
7c	C_3H_7	50
7d	CH_2-$CH(CH_3)_2$	48
7e	C_6H_5	59
7f	4-Cl-C_6H_4	56
7g	3,4-$(MeO)_2$-C_6H_3	55
7h	3,4,5-$(MeO)_3$-C_6H_2	53
7i	2-naphthyl	45

In conclusion, we have developed a convenient method for the synthesis of 4-substituted quinazolinones by PPA-induced cyclization with carboxylic acids. A variety of substituents at the 4-position of the quinazolinone skeleton were introduced readily changing carboxylic acids.

EXPERIMENTAL

Melting points were determined on a Boetius hostage apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR were measured in Bruker-250 devise by using $CDCl_3$ as solvent. Chemical shifts (δ, ppm) were referenced to TMS (δ=0.00ppm) as an internal standard and coupling constants are indicated in Hz.Unless otherwise noted, all the NMR spectra were taken at rt (ac. 295 K). MS were recorded on a Jeol JMS-D300 spectrometer (70 eV). All new compounds had correct parent ion peaks by mass spectrometry.

Polyphosphoric acid was obtained from 85% phosphoric acid and P_2O_5 (1:1 w/w).

Preparation of 1-(3,4-dimethoxyphenyl)-3-phenylurea (3): To a stirred and cooled solution of 3,4-dimethoxyaniline (2.72 g, 10 mmol) in CH_2Cl_2 (20 mL) and equimolar amount of phenylisocyanate was added dropwise. The solution was stirred for 15 min at rt to give crystalline product, which was filtered off and recrystallized from Et_2O.

Pink solid, mp 184-185°C. ^{1}H-NMR: 8.15 (1H, s, NH), 8.10 (1H, s, NH), 7.42-6.71 (8H, m, Ar), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3). ^{13}C-NMR: 153.6, 148.9, 144.5, 139.4, 132.9, 128.8, 122.3, 118.8, 111.5, 110.9, 104.3, 56.1, 55.7. MS m/z: 272 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C 66.16, H 5.92, N 10.29. Found: C 66.30, H 6.01, N 10.43.

Synthesis of 4-substituted 6,7-dimethoxy-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (7a-i); Typical procedure: 1-(3,4-dimethoxyphenyl)-3-phenylurea (**3**) (0.544 g, 2 mmol) and the corresponding carboxylic acid (3 mmol) were dissolved in CH_2Cl_2 (3-5 mL) in an open flask and polyphosphoric acid (10 g) was added. The mixture was stirred on a mechanical stirrer carefully at 80 °C for 6 h, then poured on crushed ice. The solution was carefully made basic with 25 % NH_4OH to pH 8~9, then extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. To 2 mmol of the corresponding 6,7-dimethoxy-3-phenyl-2(3*H*)-quinazolinone (**6**) in methanol 15 mL, $NaBH_4$ (4 mmol, 0.18 g) was added portionwise. The solution was stirred for 30 min at rt, than the solvent was removed under vacuum. Water (30 mL) was added to the residue and the solution was extracted with CH_2Cl_2 (3 x 20 mL), then the combined extracts were dried (Na_2SO_4) and filtered. The products were purified by column chromatography through Al_2O_3 and eluted with Et_2O or CH_2Cl_2.

6,7-Dimethoxy-4-methyl-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (7a): white solid, mp 210-213°C, ^{1}H-NMR: 8.91 (1H, s, NH), 7.41-7.26 (5H, m, Ar), 6.55 (1H, s), 6.35 (1H, s), 4.81 (1H, q, *J*=6.5 Hz, C-4), 3.82 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 1.42 (3H, d, *J*=6.5 Hz). ^{13}C-NMR: 154.1, 149.0, 144.2, 141.4, 129.8, 128.9, 127.6, 126.6, 114.6, 108.6, 98.9, 58.8, 56.4, 55.8, 21.9. MS m/z: 298 (M^+). *Anal*. Calcd for $C_{17}H_{18}N_2O_3$: C 68.44, H 6.08, N 9.39. Found: C 68.58, H 6.21, N 9.53.

6,7-Dimethoxy-4-ethyl-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (7b): white solid, mp 74-75°C**,** ^{1}H-NMR: 8.36 (1H, s, NH), 7.39-6.74 (5H, m, Ar), 6.55 (1H, s), 6.34 (1H, s), 4.66 (1H, t, *J*=6.9 Hz, C-4), 3.87 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 1.93, 2.20 (each 1H, m, $C\underline{H}_2CH_3$), 1.08 (t, 3H, $CH_2C\underline{H}_3$, *J*=7.8

Hz). MS m/z: 312 (M^+). *Anal*. Calcd for $C_{18}H_{20}N_2O_3$: C 69.21, H 6.45, N 8.97. Found: C 69.35, H 6.59, N 9.12.

6,7-Dimethoxy-4-propyl-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (7c): white solid, mp 47-50°C**,** ^{1}H-NMR: 7.63 (1H, s, NH), 7.45-7.25 (5H, m, Ar), 6.55 (1H, s), 6.32 (1H, s), 4.73 (1H, dd, *J*=4.07, 3.19 Hz, C-4), 3.85 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 1.78 (2H, m, CH_2), 1.68 (2H, m, CH_2), 0.83 (3H, t, *J*=7.21 Hz, CH_3). MS m/z: 326 (M^+). *Anal*. Calcd for $C_{19}H_{22}N_2O_3$: C 69.92, H 6.79, N 8.58. Found: C 70.05, H 6.83, N 8.68.

6,7-Dimethoxy-4-isobutyl-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (7d): white solid, mp 151-154°C**,** ^{1}H-NMR: 8.77 (1H, s, NH), 7.46-7.24 (5H, m, Ar), 6.56 (1H, s), 6.38 (1H, s), 4.72 (1H, dd, *J*=5.47, 2.98 Hz, C-4), 3.84 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 1.74-1.63 (2H, m, CH_2), 1,64-1,46 (1H, m, C<u>H</u>$(CH_3)_2$), 0.81 (6H, dd, *J*=16.88, 6.34 Hz, 2xCH_3); ^{13}C-NMR: 154.4, 148.9, 143.4, 141.9, 128.8, 126.9, 113.7, 109.3, 99.1, 61.3, 55.8, 55.5, 43.3, 24.1, 23.4, 21.8. MS m/z: 340 (M^+). *Anal*. Calcd for $C_{20}H_{24}N_2O_3$: C 70.57, H 7.11, N 8.23. Found: C 70.70, H 7.23, N 8.35.

6,7-Dimethoxy-3,4-diphenyl-3,4-dihydro-2(1*H*)-quinazolinone (7e): white solid, mp 210-211°C, ^{1}H-NMR: 8.87 (1H, s, NH), 7.28-7.13 (10H, m, Ar), 6.51 (1H, s), 6.38 (1H, s), 5.71 (1H, s, C-4), 3.75 (3H, s, OCH_3), 3.73 (3H, s, OCH_3). ^{13}C-NMR: 154.0, 149.3, 144.5, 142.2, 141.5, 129.5, 128.8, 127.9, 127.4, 126.7, 126.6, 113.1, 109.6, 98.8, 66.9, 56.4, 55.9. MS m/z: 360 (M^+). *Anal*. Calcd for $C_{22}H_{20}N_2O_3$: C 73.32, H 5.59, N 7.77. Found: C 73.45, H 5.71, N 7.90.

6,7-Dimethoxy-4-(4-chlorophenyl)-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (7f): white solid, mp 164-167°C**,** ^{1}H-NMR: 8.81 (1H, s, NH), 7.24-7.04 (9H, m, Ar), 6.41 (1H, s), 6.32 (1H, s), 5.67 (1H, s, C-4), 3.73 (3H, s, OCH_3), 3.66 (3H, s, OCH_3). ^{13}C-NMR: 153.8, 149.5, 144.7, 140.5, 133.7, 127.8, 127.7, 127.1, 119.8, 111.3, 56.3. MS m/z: 394 (M^+). *Anal*. Calcd for $C_{22}H_{19}N_2O_3Cl$: C 66.92, H 4.85, N 7.09. Found: C 67.10, H 4.95, N 7.19.

6,7-Dimethoxy-4-(3,4-dimethoxyphenyl)-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (7g): white solid, mp 204-205°C**,** ^{1}H-NMR: 8.86 (1H, s, NH), 7.30-7.12 (5H, m, Ar), 6.71-6.69 (3H, m, Ar), 6.47 (1H, s), 6.38 (1H, s), 5.66 (1H, s, C-4), 3.83 (3H, s, OCH_3), 3.74 (9H, s, 3xOCH_3). ^{13}C-NMR: 153.9, 149.3, 149.1, 148.7, 144.5, 141.5, 134.7, 129.5, 128.8, 127.8, 126.8, 119.3, 113.0, 110.9, 109.9, 109.7, 98.8, 66.8, 56.4, 55.9, 55.8. MS m/z: 420 (M^+). *Anal*. Calcd for $C_{24}H_{24}N_2O_5$: C 68.56, H 5.75, N 6.66. Found: C 68.70, H 5.86, N 6.79.

6,7-Dimethoxy-4-(3,4,5-trimethoxyphenyl)-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (7h): white solid, mp 203-206°C, ^{1}H-NMR: 8.83 (1H, s, NH), 7.26-6.97 (5H, m, Ar), 6.38 (2H, s), 6.20 (2H, s), 5.50 (1H, s, C-4), 3.68-3.52 (15H, m, 5xOCH_3). ^{13}C-NMR: 153.1, 149.0, 143.9, 141.2, 137.5, 137.0, 129.6, 128.5, 127.2, 126.2, 112.3, 109.4, 103.5, 98.5, 66.6, 60.4, 56.1, 55.6. MS m/z: 450 (M^+). *Anal*. Calcd for $C_{25}H_{26}N_2O_6$: C 66.66, H 5.82, N 6.22. Found: C 66.76, H 5.93, N 6.34.

6,7-Dimethoxy-4-(2-naphthyl)-3-phenyl-3,4-dihydro-2(1*H*)-quinazolinone (7i): white solid, mp 213-216°C, ^{1}H-NMR: 9.23 (1H, s, NH), 7.79-6.53 (12H, m, Ar), 6.41 (1H, s), 6.37 (1H, s), 5.87 (1H, s, C-4), 3.72 (3H, s, OCH_3), 3.71 (3H, s, OCH_3).; ^{13}C-NMR: 154.2, 149.4, 144.5, 141.5, 139.6, 133.0, 132.9, 129.5, 129.1, 128.8, 128.1, 127.7, 126.7, 126.2, 126.1, 125.2, 124.7, 112.8, 109.6, 98.9, 67.2, 56.4, 55.8. MS m/z: 410 (M^+). *Anal*. Calcd for $C_{26}H_{22}N_2O_3$: C 76.08, H 5.40, N 6.82. Found: C 76.20, H 5.53, N 6.91.

ACKNOWLEDGEMENTS

We acknowledge financial support from the Fund for scientific research of the Plovdiv University.

REFERENCES

1. (a) P. Y. S. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, Y. Ru, L. T. Bacheler, J. L. Meek, M. J. Otto, M. M. Rayner, Y. N. Wong, C. H. Chang, P. C. Weber, D. A. Jackson, T. R. Sharpe, and S. Erickson-Viitanen, *Science*, 1994, **263**, 380. (b) P. Y. S. Lam, Y. Ru, P. K. Jadhav, P. E. Aldrich, G. V. DeLucca, C. J. Eyermann, C. H. Chang, G. Emmett, E. R. Holler, W. F. Daneker, L. Z. Li, P. N. Confalone, R. J. McHugh, Q. Han, R. H. Li, J. A. Markwalder, S. P. Seitz, T. R. Sharpe, L. T. Bacheler, M. M. Rayner, R. M. Klabe, L. Y. Shum, D. L. Winslow, D. M. Kornhauser, D. A. Jackson, S. Erickson-Viitanen, and C. N. Hodge *J. Med. Chem.*, 1996, **39**, 3514.
2. J. E. McCusker, A. D. Main, K. S. Johnson, C. A. Grasso, and L. McElwee-White, *J. Org. Chem.*, 2000, **65**, 5216.
3. (a) G. Semple, H. Ryder, D. P. Rooker, A. R. Batt, D. A. Kendrich, M. Szelke, M. Ohta, M. Satoh, A. Nishida, S. Akuzawa, and K. Miyata, *J. Med. Chem.*, 1997, **40**, 331. (b) J. L. Castro, R. G. Ball, H. B. Broughton, M. G. N. Russell, D. Rathbone, A. P. Watt, R. Baker, K. L. Chapman, A. E. Fletcher, S. Patel, A. J. Smith, G. R. Marshall, W. Ryecroft, and V. G. Matassa, *J. Med. Chem.*, 1996, **39**, 842.
4. T. W. von Geldern, J. A. Kester, R. Bal, J. R. WuWong, W. Chiou, D. B. Dixon, and T. J. Opgenorth, *J. Med. Chem.*, 1996, **39**, 968.
5. V. T. Bandurco, C. F. Schwender, S. C. Bell, D. W. Combs, R. M. Kanojia, S. D. Levine, D. M. Mulvey, M. A. Appollina, M. S. Reed, E. A. Malloy, R. Falotico, J. B. Moore, and A. J. Tobia, *J. Med. Chem.*, 1987, **30**, 1421.
6. M. Akazome, T. Kondo, and Y. Watanabe, *J. Org. Chem.*, 1993, **58**, 310.
7. R. A. Conley, D. L. Barton, S. M. Stefanick, M. M. Lam, G. C. Lindabery, C. F. Kasulanis, S. Cesco-Cancian, S. Currey, A. C. Fabian, and S. D. Levine, *J. Heterocycl.Chem.*,1995, **32**, 761.
8. C. Apfel, D. W. Banner, D. Bur, M. Dietz, C. Hubschwerlen, H. Locher, F. Marlin, R. Masciadri, W. Pirson, and H. Stalder, *J. Med. Chem.*, 2001, **44**, 1847.
9. A. Walser, T. Flynn, C. Mason, H. Crowley, C. Maresca, B. Yaremko, and M. O'Donnell, *J. Med.*

Chem., 1991, **34**, 1209.

10. A. A. M. Abdel-Alim, A. N. A. El-Shorbagi, M. A. El-Gendy, and H. A. H. El-Shareif, *Collect. Czech. Chem. Commun.*, 1993, **58**, 1963.
11. (a) E. Chin, R. L. Cournoyer, P. F. Keitz, E. K. Lee, F. J. Lopez-Tapia, C. R. Melville, F. Padilla, and K. K. Weinhardt, *Patent* 2005, WO 2005005397 (*Chem. Abstr.*, 2005, **142**, 155966). (b) T. J. Connolly, P. F. Keitz, E. K. Lee, J. Li, F. J. Lopez-Tapia, P. F. McGrarry, C. R. Melville, D. Nitzan, C. O'Yang, F. Padilla, and K. K. Weinhardt, *Patent* 2005, WO 2005005395 (*Chem. Abstr.*, 2005, **142**, 155965).
12. J. A. J. Den Hartog, S. David, D. Jasserand, G. J. M. Van Scharrenburg, H. H. Van Stuivenberg, and T. Tuinstra, *Patent* 2005, US 2005075355, (*Chem. Abstr.*, 2005, **142**, 373993).
13. J. Vicente, J.A. Abad, J. López-Serrano, P. G. Jones, C. Nájera, and L. Botella-Segura, *Organometallics*, 2005, **24**, 5044.
14. (a) W. Schellhammer, 'Methoden der Organischen Chemie', Vol. 7/2a, ed. by E. Műller, Houben-Weyl Thieme, Stuttgart, 1973, p. 281. (b) B. Staskun, *J. Org.Chem.*, 1964, **29**, 2856.
15. A. P. Venkov and I. I. Ivanov, *Tetrahedron*, 1996, **52**, 12299.
16. I. I. Ivanov, St. A. Nikolova, and St. M. Statkova-Abeghe, *Heterocycles*, 2005, **68**, 369.