NEW 4(3*H*)-QUINAZOLINONIUM SALTS WITH POTENTIAL BIOLOGICAL ACTIVITY

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Bromurile de chinazoliniu au fost sintetizate cu randamente bune, pornind de la chinazolinononă şi derivaţii bromuraţi. Compuşii pot constitui o serie pentru studiul acitivităţii biologice.

The quinazolinonium bromides were obtained in good yields by reacting the corresponding quinazolinone with brominated derivatives. The compounds could provide a library for further studies on their biological activity.

Keywords: 3(4*H*)-quinazolinonium salts, NMR spectroscopy, biological activity

1. Introduction

Quinazolinones are of particular interest due to their enhanced biological activity [1] such as antimicrobial and anti-inflammatory [2,3], antitumour activity [4-6] or antidepressant [7]. Furthermore applications as pesticides are known [8]. Other properties such as fluorescence [9] for example, are also studied for potential applications. Furthermore synthesis and biological properties of quinazolinonium salts are reported in the literature [10]. Such types of compounds are reported to show important antimicrobial activity. The literature shows that the 3-R-4(3*H*)-quinazolinonium salts alkylated at the N1 nitrogen atom were obtained by two methods. The first method implies the cyclization of the *N*-benzylanthranilic acid derivatives [10] and the second by the alkylation of the 2-methyl-3-phenyl-4(3*H*)-quinazolinone with trimethylsilylmethyltriflate [11]. In

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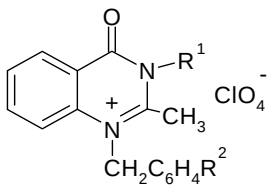
both cases, the obtained salts have a methyl group attached in position 2 according to formulae **1** and **2**.



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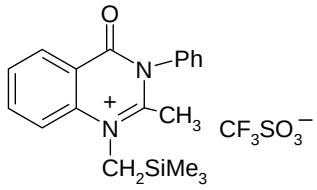

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Our interest in obtaining new pyrroloazines [12-21], especially new pyrroloquinazolines [22-27], led us to investigate the possibility of obtaining the pyrrolo[1,2-a]quinazoline skeleton by 1,3-dipolar cycloaddition reaction starting from quinazolinonium salts. Pyrrolo[1,2-a]quinazolinones are known for their interesting biological properties [28-30]. In the literature there are known some studies on obtaining pyrrolo[1,2-a]quinazolinones starting from quinazolinonium salts *via N*-ylide intermediates, but the authors reported that only substituted *N*-arylpyrroles are obtained [11, 15].

Herein is presented the synthesis and characterization of new quinazolinonium salts which could provide a library for further studies on their biological properties.

2. Experimental

General

Melting points were determined on a Boëtius hot plate and are uncorrected. The IR spectra were recorded on FT-IR Bruker Vertex 70 spectrometer. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C.

General procedure for obtaining the 4(3*H*)quinazolinonium bromides **5**

10 Mmol 3-Methyl-4(3H)quinazolin-4-one **3** and 10 Mmol 2-bromoaroyl **4** in 30 mL ethanol or isopropanol was stirred under reflux for 20 h. The obtained precipitate was filtered and then crystallized from methanol.

1-[2-(4-Fluorophenyl)-2-oxoethyl]-3-methyl-4(3*H*)quinazolinon-1-ium bromide (**5a**)

Colorless crystals with mp. 248-9 °C were obtained by crystallization from methanol; Yield 78%. Anal. Calcd. $C_{17}H_{14}BrFN_2O_2$: N 7.43. Found: N 7.24. FT-IR (cm^{-1}): 1652, 1690, 1708, 2930, 3050.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.87(s, 3H, MeN); 6.38 (s, 2H, CH_2); 7.22-7.28 (m, 2H, H-3', H-5'); 7.42 (d, 1H, *J* = 8.5 Hz, H-8); 7.82 (t, 1H, *J* = 7.8 Hz, H-6); 7.97 (dt, 1H, *J* = 8.5 Hz, 1.65 Hz, H-7); 8.16 -8.21 (m, 2H, H-2', H-6'); 8.51 (dd, 1H, *J* = 7.8 Hz, 1.65 Hz, H-5) 9.94 (s, 1H, H-2).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 36.8 (MeN); 58.5 (CH_2); 117.4 (C-8); 129.3 (C-5); 129.5 (C-3', C-5'); 130.7 (C-6); 131.8 (C-2', C-6'); 119.6, 129.3, 137.4 (C-4a, C-8a, C-1'); 137.7 (C-7); 154.3 (C-2); 169.0 (C-4'); 157.7 (CON); 188.3 (COAr).

1-[2-(4-Chlorophenyl)-2-oxoethyl]-3-methyl-4(3*H*)quinazolinon-1-ium bromide (**5b**)
Colorless crystals with mp. 276-8 °C were obtained by crystallization from methanol; Yield 81%. Anal. Calcd. $C_{17}H_{14}BrClN_2O_2$: N 7.12. Found: N 7.40. FT-IR (cm^{-1}): 1298, 1496, 1650, 1693, 1712, 2932, 3054.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.87 (s, 3H, MeN); 6.39 (s, 2H, CH_2); 7.42 (d, 1H, *J* = 8.5 Hz, H-8); 7.55 (d, 2H, *J* = 8.5 Hz, H-3', H-5'); 7.83 (t, 1H, *J* = 7.8 Hz, H-6); 7.98 (dt, 1H, *J* = 8.5 Hz, 1.65 Hz, H-7); 8.09 (d, 2H, *J* = 8.5 Hz, H-2', H-6'); 8.52 (dd, 1H, *J* = 7.8 Hz, 1.6 Hz, H-5) 10.04 (s, 1H, H-2).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 36.8 (MeN); 58.5 (CH_2); 117.4 (C-8); 129.6 (C-5); 129.9 (C-3', C-5'); 130.2 (C-2', C-6'); 130.8 (C-6); 119.6, 131.0, 142.8(C-4a, C-8a, C-1'); 137.5 (C-7); 137.7 (C-4'); 154.3 (C-2); 157.5 (CON); 188.9 (COAr).

1-[2-(4-Bromophenyl)-2-oxoethyl]-3-methyl-4(3*H*)quinazolinon-1-ium bromide (**5c**)
Colorless crystals with mp. 284-6 °C were obtained by crystallization from methanol; Yield 81%. Anal. Calcd. $C_{17}H_{14}Br_2N_2O_2$: N 6.39. Found: N 6.60. FT-IR (cm^{-1}): 1298, 1496, 1651, 1693, 1715, 2935.
^{1}H-NMR (300 MHz, DMSO-d6) δ: 3.68 (s, 3H, MeN); 6.46(s, 2H, CH_2); 7.82-7.86 (m, 1H, H-6); 7.91 (d, 2H, J = 8.8 Hz, H-3', H-5'); 7.98 (d, 1H, *J* = 8.5 Hz, H-8); 8.04-8.11 (m, 3H, H-7, H-2', H-6'); 8.39 (d, 1H, *J* = 7.8 Hz, H-5); 10.05 (s, 1H, H-2).
^{13}C-NMR (75 MHz, DMSO-d6) δ: 36.3 (MeN); 58.1 (CH_2); 118.9 (C-8); 127.8 (C-5); 130.4, 132.1 (C-2', C-3', C-5', C-6'); 129.0 (C-6); 119.1, 129.9, 142.8 (C-4a, C-8a, C-1'); 136.7 (C-7); 138.0 (C-4'); 155.1 (C-2); 157.8 (CON); 190.0 (COAr).

1-[2-(4-Methylphenyl)-2-oxoethyl]-3-methyl-4(3*H*)quinazolinon-1-ium bromide (**5d**)

Colorless crystals with mp. 264-6 °C were obtained by crystallization from methanol; Yield 76%. Anal. Calcd. $C_{18}H_{17}BrN_2O_2$: N 7.51. Found: N 7.24. FT-IR (cm^{-1}): 1295, 1494, 1699, 1710, 2927, 3033.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.42, 3.87(2s, 6H, 2Me); 6.37 (s, 2H, CH_2); 7.32 (d, 2H, , *J* = 8.2 Hz, H-3', H-5'); 7.43 (d, 1H, *J* = 8.5 Hz, H-8); 7.78 (t, 1H, *J* = 7.8 Hz, H-6); 7.93-7.99 (m, 3H, H-7, H-2', H-6'); 8.46 (dd, 1H, *J* = 7.8 Hz, 1.6 Hz, H-5) 10.16 (s, 1H, H-2).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 21.8 (Me); 36.7 (MeN); 58.5 (CH_2); 117.5 (C-8); 129.3 (C-5); 128.8 (C-2', C-6'); 130.5 (C-6, C-3', C-5'); 119.6, 130.2, 137.7 (C-4a, C-8a, C-1'); 137.7 (C-7); 154.3 (C-2); 147.4 (C-4'); 157.6 (CON); 189.3 (COAr).

1-(2-Biphenylyl-2-oxoethyl)-3-methyl-4(3*H*)quinazolinon-1-ium bromide (**5e**)
Colorless crystals with mp. 266-267 °C were obtained by crystallization from methanol; Yield 80%. Anal. Calcd. $C_{23}H_{21}BrN_2O_2$: N 6.44. Found: N 6.71. FT-IR (cm^{-1}): 1296, 1494, 1689, 1712, 2934, 3029.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.88(s, 3H, MeN); 6.39 (s, 2H, CH_2); 7.44 (d, 1H, *J* = 8.5 Hz, H-8); 7.46-7.53 (m, 7H, ByPh); 7.63-7.66 (m, 2H, ByPh); 7.82 (t, 1H, *J* = 7.8 Hz, H-6); 7.97 (dt, 1H, *J* = 8.5 Hz, 1.65 Hz, H-7); 8.52 (dd, 1H, *J* = 7.8 Hz, 1.65 Hz, H-5) 9.93 (s, 1H, H-2).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 37.0 (MeN); 58.7 (CH_2); 117.4 (C-8); 127.5, 128.1, 129.2, 129.3 (C-2', C-3', C-5', C-6', C-2", C-3", C-4", C-5", C-6"); 129.6 (C-5); 131.0 (C-6); 119.7, 129.5, 131.1, 137.6 149.1 (C-4a, C-8a, C-1', C-4', C-1"); 137.7 (C-7); 154.5 (C-2); 157.8 (CON); 189.9 (COAr).

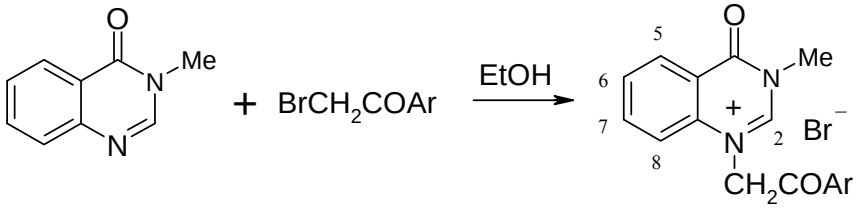
1-[2-(2-Nitrophenyl)-2-oxoethyl]-3-methyl-4(3*H*)quinazolinon-1-ium bromide (**5f**)
Colorless crystals with mp. 226-8 °C were obtained by crystallization from methanol; Yield 68%. Anal. Calcd. $C_{17}H_{14}BrN_3O_2$: N 10.40. Found: 10.69. FT-IR (cm^{-1}): 1295, 1350, 1495, 1653, 1710, 2946, 3050.
^{1}H-NMR (300 MHz, DMSO-d6) δ: 3.77 (s, 3H, MeN); 6.45 (s, 2H, CH_2); 7.88-7.92 (m, 1H, H-6); 7.95-7.98 (m, 1H, Ar); 8.04 (d, 1H, *J* = 8.5 Hz, H-8); 8.06-8.09 (m, 1H, H-7); 8.17-8.22 (m, 1H, Ar); 8.40 (d, 1H, *J* = 7.8 Hz, H-5); 10.43 (s, 1H, H-2).
^{13}C-NMR (75 MHz, DMSO-d6) δ: 36.3 (MeN); 59.3 (CH_2); 118.1 (C-8); 124.7 (C-4'); 128.0 (C-5); 129.2 (C-6'); 130.0 (C-6); 119.2, 131.3, 146.0(C-4a, C-8a, C-1'); 133.3 (C-3'); 134.4 (C-5'); 136.7 (C-7); 137.6.1 (C-2'); 155.3 (C-2); 157.8 (CON); 192.6 (COAr).

1-[2-(3-Coumaryl)-2-oxoethyl]-3-methyl-4(3*H*)quinazolinon-1-ium bromide (**5g**)

Colorless crystals with mp. 249-250 °C were obtained by recrystallization from methanol; Yield 78%. Anal. Calcd. $C_{20}H_{15}BrN_2O_4$: N 6.56. Found: 6.88. FT-IR (cm^{-1}): 1187, 1293, 1498, 1689, 1715,1720, 2947, 3034.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.88(s, 3H, MeN); 6.46 (s, 2H, CH_2); 7.30-7.41 (m, 2H, 2H-Coumaryl); 7.62 (d, 1H, *J* = 8.5 Hz, H-8); 7.70-7.79 (m, 3H, H-6, 2H-Coumaryl); 7.92-7.97 (m, 1H, H-7); 8.45 (dd, 1H, *J* = 7.8 Hz, 1.65 Hz, H-5); 8.72 (s, 1H, 1H-Coumaryl); 10.24 (s, 1H, H-2).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 36.7 (MeN); 61.2 (CH_2); 116.9 (1C-Coumaryl); 118.1 (C-8); 126.0 (1C-Coumaryl); 129.4 (C-5); 130.6 (1C-Coumaryl); 131.3 (C-6); 118.0, 119.6, 129.3, 137.2, 137.8, 155.4 (C-4a, C-8a, C-1', 3C-Coumaryl); 137.4 (C-7); 151.5 (1C-Coumaryl); 154.5 (C-2); 157.8 (CON); 188.7 (COAr).

3. Discussion

Quinazolinium *N1*-salts are generally unavailable, due to the decreased reactivity of nitrogen atom N1 as compared to N3 [31,32]. To overcome this impediment, the starting material used was 3-methyl-4(3*H*)-quinazolinone **3**, instead of quinazoline. Quaternization of nitrogen atom N1 with bromoacetophenones **4** was performed in ethanol or isopropanol under reflux, resulting in salts **5** in yields exceeding 75% (Scheme 1).



3 **4a-g** **5a-g**

Ar: **a**: 4-FC_6H_4; **b**: 4-ClC_6H_4; **c**: 4-BrC_6H_4; **d**: 4-MeC_6H_4; **e**: 4-$C_6H_5C_6H_4$; **f**: 2-$NO_2C_6H_4$: g: $C_{11}H_7O_3$-

Scheme 1

The new compounds were characterized by IR and NMR spectroscopy. The NMR spectra are in good agreement with the structure of the compounds.

The first evidence of the structure of the new compounds is provided by IR spectroscopy. Thus, the main characteristic of the compounds is the presence of the carbonyl bands at 1650-1690 cm^{-1} for the COAr and 1708-1712 cm^{-1} for the CO group in the pyrimidinic ring. Also the carbonyl group in the coumaryl moiety appears at 1715 cm^{-1} and at 1187cm^{-1} the band of the simple bond C-O.

The methyl group directly bonded to the nitrogen atom appears as a singlet at ~3.87 ppm while the signal of the methylene group appears as a deshielded singlet at about 6.40 ppm due to its direct bond to a nitrogen atom and a carbonyl group. The hydrogen atoms H-6, H-7 and H-8 appear in normal ranges with a predicted multiplicity. The hydrogen H-5 appears deshielded due to its spatial vicinity of the carbonyl group, having the multiplicity doublet of doublets with the coupling constants J_{H5H6} = 7.8 Hz and J_{H5H7} = 1.6. The most deshielded proton is the H-2 due to its spatial vicinity with two nitrogen atoms. The H-2 hydrogen appears as a singlet at around 10 ppm. Fig. 1 presents the ^{1}H-NMR spectrum of the compound **5b**. The coumaryl moiety of the compound **5g** present in its spectrum the singlet at 8.71 ppm and the signals of the other four hydrogen atoms in the range 7.30-7.70 ppm. The spectra of compounds **5c** and **5f** were performed in DMSO-d6 which induces some slight differences in comparison with the spectra of the other compounds in $CDCl_3$, mainly regarding the chemical shifts of the atoms H-6 and H-8.

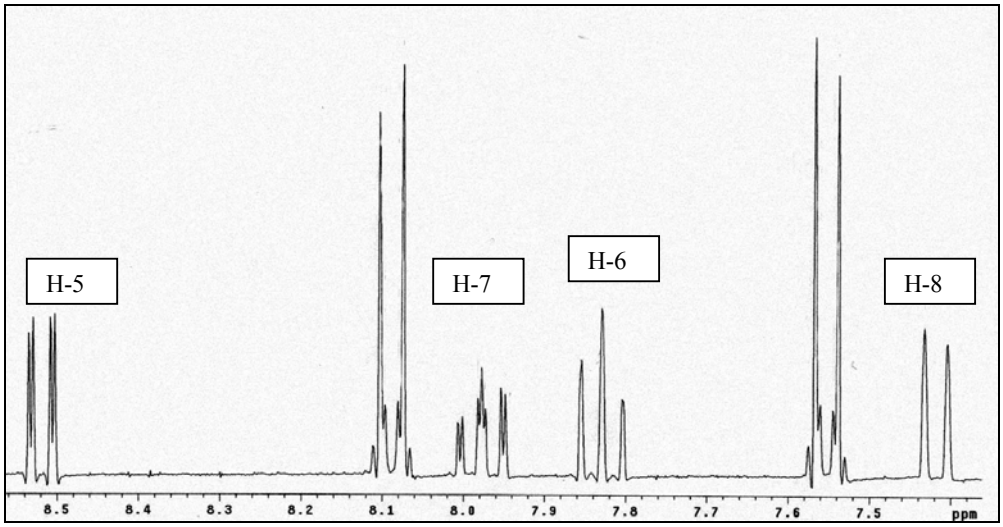


Fig.1. The ^{1}H-NMR spectrum (in $CDCl_3$) of compound **5b** - aromatic region without H-2 at 10 ppm

The ^{13}C-NMR spectra of the compounds present as main characteristic features the signals of the two carbon atoms in the carbonyl groups at ~190 ppm (COAr) and ~160 ppm (CON). The methyl group directly bonded to the nitrogen atom presents its signal at 36.8 ppm while the carbon atom in the methylene group appears at about 60 ppm. Similar to the hydrogen H-2 which appears deshielded, the carbon C-2 appears strongly deshielded to ~154 ppm due to its direct bonding with two nitrogen atoms. The carbon atom C-8 appears strongly shielded at ~ 118

ppm due to its relative position to the shielding cone of the carbonyl group in the aroyl moiety.

4. Conclusions

In conclusion 6 new quinazolinonium salts were obtained starting from the corresponding quinazolinone and different bromides. Structural variety was conferred by varying the aromatic bromides employed. The compounds were characterized by IR and NMR spectroscopy. Further studies on the biological activity of such types of compounds could be performed.

Acknowledgement

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R E F E R E N C E S

[1]. *N.I. Chernobrovin, Yu. V. Kozhevnikov, G.E. Morozova, T.A. Chernobrovina*, J. Pharm. Chem. 1992, 26, 245
[2]. O.L. Vizgunova, Yu.V. Kozhevnikov, L.M. Obvintseva, V.S. Zalesov, J. Pharm. Chem. 1987, 20, 614
[3]. *O.E. Sattarova, O.L. Vizgunova, É.V. Voronina*, J. Pharm. Chem. 2006, 40, 73
[4]. *K. Hattori, Y. Kido, H. Yamamoto, J. Ishida, A. Iwashita, K. Mihara*, Bioorg. Med. Chem. Lett. 2007, 17, 5577
[5]. *A. Kamal, E.V. Bharathi, M.J. Ramaiah, D. Dastagiri, J.S. Reddy, A. Viswanath, F. Sultana, S.N.C.V.L. Pushpavalli, M. Pal-Bhadra , H.K. Srivastava, G.N. Sastry, A. Juvekar, S. Sen, S. Zingde*, Bioorg. Med. Chem. 2010, 18, 526
[6]. *R.S. Giri, H.M. Thaker, T. Giordano, B. Chen, S. Nuthalapaty, K.K. Vasu,V. Sudarsanam*, Eur. J. Med. Chem. 2010, 45, 3558
[7]. *Y.H. Na, S.H. Hong, J.H. Lee, W.-K. Park, D.-J. Baek, H.Y. Koh, Y.S. Cho, H. Chooa, A.N. Paea*, Bioorg. Med. Chem. 2008, 16, 2570
[8]. *C. Ye, J. You, X. Li, R. You, Y. Weng, J. Li, Y.Wang*, Pesticide Biochemistry and Physiology 2010, 97, 194
[9]. *X.-B. Zhang , G. Cheng, W.-J. Zhang, G.-L. Shen, R.-Q. Yu*, Talanta 2007, 71, 171
[10]. *N.I. Chernobrovin, Yu.V. Kozhevnikov, V.S. Zalesov and I.I. Gradel'*, J. Pharm. Chem. 1985, 18, 485
[11] *M. Azouz, K. Lamara, M. Teguiche, R.K. Smalley*, Asian J. Chem. 2008, 20, 954
[12]. *E. Georgescu, F. Dumitrascu, F. Georgescu, C. Draghici, M.M. Popa*, Rev. Roum. Chim. 2010, 55, 217
[13]. *F. Dumitrascu, M.T. Caproiu, F. Georgescu, B. Draghici, M.M. Popa, E. Georgescu*, Synlett 2010, 2407
[14]. *F. Dumitrascu, C. Draghici, M.T. Caproiu, D.G. Dumitrescu, M.M. Popa*, Rev. Roum. Chim. 2009, 53, 923.

[15]. *F. Dumitrascu, E. Georgescu, M.R. Caira, F. Georgescu, M. Popa, B. Draghici, D.G. Dumitrescu*, Synlett 2009, 3336
[16]. *E. Georgescu, M.R. Caira, F. Georgescu, B. Draghici, M.M. Popa, F. Dumitrascu*, Synlett 2009, 1795
[17]. M. R. Caira, E. Georgescu, F. Georgescu, M. M. Popa, F. Dumitrascu, Arkivoc 2009, (xii), 242
[18]. *M.T. Caproiu, F. Dumitrascu, M.R. Caira*, Rev. Chim. (Bucharest) 2008, 59, 1242
[19]. *F. Dumitrascu, M.R. Caira, B. Draghici, M.T. Caproiu, D.G. Dumitrescu*, Synlett 2008, 813
[20]. F. *Dumitrascu, C.I. Mitan, C. Drăghici, M.T. Căproiu, D. Răileanu*, Tetrahedron Lett. 2001, 41, 8379
[21] *F. Dumitrascu, M.R. Caira, C. Draghici, M.T. Caproiu, L. Barbu*, Rev. Chim. (Bucuresti) 2009, 60, 851
[22] *E. Georgescu, I. Druta, M. Petrovanu*, Rev. Roum. Chim., 1981, 26, 109
[23] *E. Georgescu, I. Druta, M. Petrovanu*, Bull. Inst. Politehnic Iasi, 1981, XXVII, (3-4), Sect. II, 81
[24] *E. Georgescu, F. Georgescu, M. Gheorghiu, E.G. Georgescu, M. Petrovanu*, Rev. Roum. Chim., 1985, 30, 611
[25] *F. Georgescu, E. Georgescu, C. Draghici, M.T. Caproiu*, Rev. Roum. Chim., 1997, 42, 17.
[26] *E. Georgescu, F. Georgescu, C. Roibu, P.C. Iuhas, C. Draghici, P. Filip*, Arkivoc, 2008, (xii), 60
[27] *E. Georgescu, F. Georgescu, M.R. Caira, A. Nicolescu, C. Deleanu, M. Danila, P. Filip, F. Dumitrascu*, Arkivoc, 2009, (xii), 232
[28]. *E. Wolf and B. Duffy*, US Patent 3883524; Chem. Abstr., 83, 131624 (1975)
[29]. *F. Ishikawa, A. Kosasayama, and K. Abiko*, Jpn. Patent 7844593; Chem. Abstr., 89, 194584 (1978)
[30]. *M. Suesse*, E. German Patent 142333; Chem. Abstr., 94, 175162 (1981)
[31] *W.L.F. Armarego*, "Advances in Heterocyclic Chemistry" (ed. A.R. Katritzky). **Vol. 1**, 1963, 253
[32] *E. Georgescu, F. Georgescu, F. Chiraleu, M. Petrovanu*, Rev. Roum. Chim., 1983, 28 (8), 841.