# New Pyrrolo[2,1-*a*]phthalazine Derivatives by One-Pot Three-Component Synthesis

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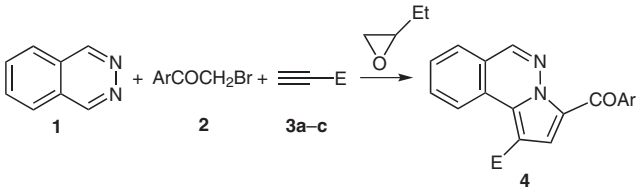
**Abstract:** The synthesis of the pyrrolo[2,1-*a*]phthalazine derivatives was performed by an efficient one-pot three-component reaction starting from phthalazine, 2-bromoacetophenones and nonsymmetrical and symmetrical acetylenic dipolarophiles in 1,2-epoxybutane as both reaction medium and HBr scavenger. The structure of the compounds was assigned by IR and NMR spectroscopy.

**Key words:** 1,3-dipolar cycloaddition, *N*-ylide, pyrrolo[2,1-*a*]-phthalazine, multicomponent reaction

Pyrrolo[2,1-*a*]phthalazines are nitrogen-containing heterocyclic compounds which are of great interest due to their biological activity and optical properties.[1]

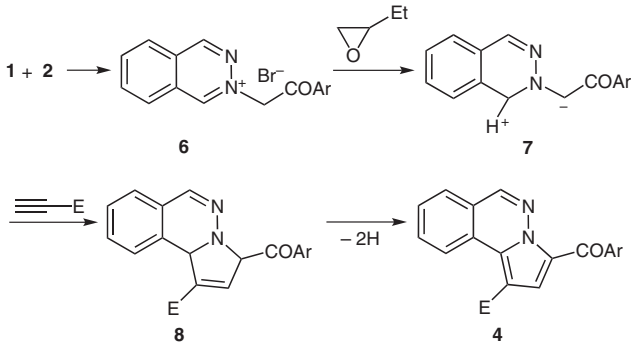
There have been reported two main synthetic strategies used in the preparation of pyrrolo[2,1-*a*]phthalazines starting either from phthalazine or pyrroles[2] and only one synthesis starting from acyclic compounds.[3] The known synthesis of pyrrolo[2,1-*a*]phthalazines via phthalazinium *N*-ylides[4] involves a two-stage process which implies the preparation and separation of the phthalazinium salts which are subsequently converted into pyrrolo[2,1-*a*]-phthalazines by treatment with a base, to generate the corresponding phthalazinium *N*-ylide in the presence of acetylenic dipolarophile.

Syntheses involving multicomponent and one-pot reactions are of interest because they involve straightforward one-step transformations starting from three or more components.[5] Our interest in obtaining new pyrroloazines by conventional methods or by multicomponent one-pot reactions[6] has led us to extend our studies to pyrrolo[2,1-*a*]phthalazines. Herein is presented for the first time the three-component, one-pot synthesis of pyrrolo[2,1-*a*]-phthalazine derivatives starting from commercially available materials. The key components are phthalazine **1**, the substituted bromoacetophenones **2**, the nonsymmetrical electron-deficient alkynes **3** and 1,2-epoxybutane which acts both as solvent and as proton scavenger (Scheme 1). The reaction takes place under mild conditions and involves the mixing of the components at reflux for 12 hours, followed by partial solvent evaporation.[7] The compounds **4** were obtained in yields of 61–75%.




**Scheme 1** One-pot synthesis of pyrrolo[2,1-*a*]phthalazines **4**

The reaction mechanism implies the intermediate formation of the phthalazinium salt **6** from the corresponding phthalazine and 2-bromoacetophenone. In the next step, the bromide ion from the salts attacks the oxirane ring of 1,2-epoxybutane, resulting in ring opening with formation of an alkoxide that generates the phthalazinium *N*-ylide **7**. The *N*-ylide reacts with the activated alkyne **3** to give the corresponding dihydropyrrolophthalazine **8**. Finally, the pyrrolophthalazines **4a–o** are obtained by the spontaneous in situ dehydrogenation of the dihydropyrrolophthalazine intermediate (Scheme 2).




**Scheme 2** The mechanism of the synthesis of compounds **4**

The substituents of the new pyrrolo[2,1-*a*]phthalazine derivatives **4** are given in Table 1.

The structures of the compounds **4** were assigned by elemental analysis, IR and NMR spectroscopy. The characteristic IR spectroscopic features of the compounds **4** were the carbonyl bands observed in the range 1690–1725 $cm^{-1}$ for the carboxyl groups and in the range 1649–1680 $cm^{-1}$ for the carbonyl group in the benzoyl moiety due to conjugation. The C–O vibration specific bands could be ob-

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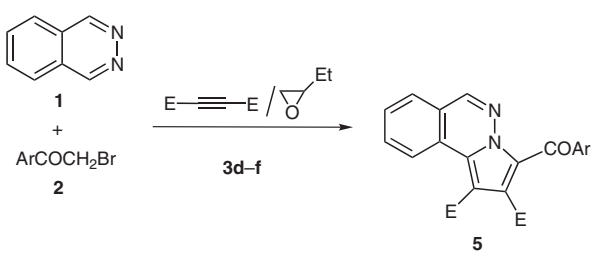
**Table 1** Substituents of the Pyrrolo[2,1-*a*]phthalazine Derivatives **4**

| Compound | E | Ar | Mp (°C) |
|---|---|---|---|
| **4a** | COMe | Ph | 205–207 |
| **4b** | COMe | 4-$BrC_6H_4$ | 197–201 |
| **4c** | COMe | 4-$MeOC_6H_4$ | 158–160 |
| **4d** | COMe | 3-$O_2NC_6H_4$ | 230–232 |
| **4e** | COMe | 4-$O_2NC_6H_4$ | 273–274 |
| **4f** | $CO_2Me$ | $C_6H_4C_6H_5$ | 207–210 |
| **4g** | $CO_2Me$ | 4-$MeC_6H_4$ | 220–222 |
| **4h** | $CO_2Me$ | 4-$FC_6H_4$ | 230–233 |
| **4i** | $CO_2Me$ | 3-$BrC_6H_4$ | 196–198 |
| **4j** | $CO_2Me$ | 4-$BrC_6H_4$ | 207–210 |
| **4k** | $CO_2Me$ | 3-$O_2NC_6H_4$ | 238–239 |
| **4l** | $CO_2Et$ | $C_6H_4C_6H_5$ | 210–211 |
| **4m** | $CO_2Et$ | 2-$ClC_6H_4$ | 220–223 |
| **4n** | $CO_2Et$ | 3-$BrC_6H_4$ | 177–179 |
| **4o** | $CO_2Et$ | 4-$O_2NC_6H_4$ | 160–162 |

served at ca. 1080 $cm^{-1}$ and ca. 1230 $cm^{-1}$. The C=O bond in the acyl moiety for the compounds **4a–e** appeared at around 1672 $cm^{-1}$. The $^1H$ NMR spectra of compounds **4** confirmed the regioselectivity of the cycloaddition as the hydrogen H-2 appeared as a sharp singlet at ca. δ = 7.70 ppm. At high resolution the hydrogen H-6 appeared as a doublet with a coupling constant of $^5J_{H6H10} = 0.8$ Hz which is consistent with a long-range coupling between H-6 and H-10, confirmed by HH decoupling experiments. The H-10 atom was strongly deshielded (δ = ca. 9.80 ppm) due to the proximity of the carbonyl group attached to the position 1.

The $^{13}C$ NMR spectra showed all the expected signals. The spectra of pyrrolophthalazines presented the signals of the carbonyl groups as are expected for compounds with this structure. The carbon C-6 grafted on a double C–N bond in the phthalazine moiety appeared strongly deshielded (δ = ca. 146 ppm) whereas the C-1 in the pyrrole ring appeared shielded due the substituent directly attached (δ = ca. 117 ppm for compounds **4a–e** and δ = ca. 108 ppm **4f–o**).

Recently we reported that the one-pot method for synthesis of pyrrolo[1,2-*a*]quinolines gave very poor yields when using symmetrical dipolarophiles, because of the poor reactivity of the quinoline with 2-bromoacetophenones.[6c,d] However, in the case of phthalazine the one-pot reaction could be realized using symmetrical dipolarophiles. Therefore, a procedure that avoids the isolation of phthalazinium bromides was elaborated, by taking into account the high reactivity of the phthalazine, compared with quinoline, towards the 2-bromoacetophenones. The modified procedure consists of adding the key components of the reaction in a specific order. Thus the 2-bromoacetophenones were added to the solution of phthalazine in 1,2-epoxybutane and the mixture was kept under stirring for 30 minutes before the acetylenic dipolarophile was added.[8] One of the symmetrical acetylenic dipolarophiles, the diisopropyl acetylenedicarboxylate (DIPAD) was synthesized by a similar procedure reported in *Organic Synthesis* for dimethyl acetylenedicarboxylate (DMAD) and diethyl acetylenedicarboxylate (DEAD).[9] Thus, the pyrrolo[2,1-*a*]phthalazines **5** were obtained in good yields ranging between 61–80% (Scheme 3).




**Scheme 3** One-pot synthesis of pyrrolo[2,1-*a*]phthalazines **5**

The reaction between phthalazinium *N*-ylides and symmetrical acetylenic dipolarophiles in different solvents such as dichloromethane or benzene frequently gave mixtures of dihydropyrrolophthalazine with pyrrolophthalazine.[1g,4d–f,10] In such cases the aromatization of the hydrogenated intermediate was achieved with the oxidant tetrakispyridine cobalt(II) dichromate (TPCD)[4e,f] which was also used for aromatization of tetrahydro cycloadducts resulting from activated olefins and heteroaromatic *N*-ylides.[11] The one-pot multicomponent approach described here avoids the formation of the hydrogenated in-

**Table 2** Substituents on Compounds **5**

| Compound | E | Ar | Mp (°C) |
|---|---|---|---|
| **5a** | $CO_2Me$ | Ph | 229–231 |
| **5b** | $CO_2Me$ | 4-$MeC_6H_4$ | 192–194 |
| **5c** | $CO_2Me$ | 4-$ClC_6H_4$ | 176–178 |
| **5d** | $CO_2Me$ | 3-$BrC_6H_4$ | 181–183 |
| **5e** | $CO_2Me$ | 4-$BrC_6H_4$ | 178–180 |
| **5f** | $CO_2Et$ | Ph | 125–127 |
| **5g** | $CO_2Et$ | 4-$FC_6H_4$ | 153–155 |
| **5h** | $CO_2Et$ | 4-$ClC_6H_4$ | 153–154 |
| **5i** | $CO_2Et$ | 4-$BrC_6H_4$ | 168–169 |
| **5j** | $CO_2Et$ | 4-$O_2NC_6H_4$ | 163–165 |
| **5k** | $CO_2i$-Pr | 4-$MeC_6H_4$ | 147–148 |
| **5l** | $CO_2i$-Pr | 4-$ClC_6H_4$ | 148–150 |
| **5m** | $CO_2i$-Pr | 4-$BrC_6H_4$ | 168–169 |

termediates leading directly to the fully aromatic compounds.

Table 2 lists the substituents on compounds **5**.

The compounds were characterized by elemental analysis, IR and NMR spectroscopy. It was observed that the substituent attached at C-2 influences the spatial interaction between the carbonyl bond attached at C-1 and the hydrogen H-10 which appears shielded by ca. 1 ppm in compounds **5** compared to compounds **4**. It must be mentioned that the pyrrolo[2,1-*a*]phthalazine derivatives **5** could be prepared by a one-pot procedure starting directly from the phthalazinium bromides obtained in a previous step and acetylenic dipolarophiles in 1,2-epoxybutane.

In summary, a library of pyrrolo[2,1-*a*]phthalazine derivatives was obtained by a simple one-pot three-component reaction of phthalazine with 2-bromoacetophenones and symmetrical and nonsymmetrical electron-deficient alkynes in 1,2-epoxybutane.

## References and Notes


(1) (a) Ashton, M. C.; Bridge, A. W.; Dron, D. I.; Fenton, G.; Lythgoe, D. J.; Newton, C. G. Eur. Patent Appl., EP 319330, **1988**; *Chem. Abstr.* **1989**, *111*, 232846u. (b) Caprosu, M.; Stefanescu, E.; Ungureanu, M.; Petrovanu, M. *Rev. Roum. Chim.* **1991**, *36*, 657. (c) Kidena, H.; Hirayama, N.; Hotsuta, M.; Meguro, S.; Yoshizuka, N.; Ichinose, S.; Nishizawa, Y. Jpn. Kokai Tokkyo Koho Jpn. Patent, JP0565215, **1993**; *Chem. Abstr.* **1993**, *119*, 34097c. (d) Cheng, Y.; Ma, B.; Wudl, F. *J. Mater. Chem.* **1999**, *9*, 2183. (e) Mitsumori, T.; Bendikov, M.; Sedó, J.; Wudl, F. *Chem. Mater.* **2003**, *15*, 3759. (f) Uff, B. C.; Ghaem-Maghami, G.; Budhram, R. S.; Wilson, C. L.; Apatu, J. O. *J. Heterocycl. Chem.* **1989**, *26*, 571. (g) Butnariu, R. M.; Caprosu, M. D.; Bejan, V.; Ungureanu, M.; Poiata, A.; Tuchilus, C.; Florescu, M.; Mangalagiu, I. *J. Heterocycl. Chem.* **2007**, *44*, 1. (h) Dorweiler, C.; Holderbaum, M.; Munzmay, T.; Spang, P.; Durr, H.; Kruger, C.; Raabe, E. *Chem. Ber.* **1988**, *121*, 843.

(2) (a) Uff, B. C.; Budhram, R. S. *Synthesis* **1978**, 206. (b) Potts, K. T.; Bordeaux, K. G.; Kuehnling, W. R.; Salsbury, R. L. *J. Org. Chem.* **1985**, *50*, 1677. (c) Weidner, C. H.; Michaels, F. M.; Beltman, D. J.; Montgomery, C. J.; Wadsworth, D. H.; Briggs, B. T.; Picone, M. L. *J. Org. Chem.* **1991**, *56*, 5594. (d) Bridge, A. W.; Hursthouse, M. B.; Lehmann, C. W.; Lythgoe, D. J.; Newton, C. G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1839. (e) Siriwardana, A. I.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 3202. (f) Galin, F. Z.; Sakhautdinov, I. M.; Tukhavatullin, O. R. *Russ. Chem. Bull. Int. Ed.* **2007**, *53*, 2305.

(3) Sharp, J. T.; Wilson, P.; Parsons, S.; Gould, R. O. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1139.

(4) (a) Khlebnikov, A. F.; Kostik, E. I.; Kostikov, R. R. *Synthesis* **1993**, 568. (b) Butler, R. N.; Coyne, A. G.; Burke, L. A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1781. (c) Komatsu, M.; Kasano, Y.; Yamaoka, S.; Minakata, S. *Synthesis* **2003**, 1398. (d) Dumitrascu, F.; Mitan, C. I.; Draghici, C.; Caproiu, M. T.; Raileanu, D. *Tetrahedron Lett.* **2001**, *42*, 8379. (e) Dumitrascu, F.; Alecu, M.; Badoiu, A.; Vuluga, D. *Rev. Chim. (Bucharest)* **2003**, *54*, 974. (f) Dumitrascu, F.; Draghici, C.; Caproiu, M. T.; Dumitrescu, D.; Badoiu, A. *Rev. Roum. Chim.* **2006**, *51*, 643. (g) Dumitrascu, F.; Caira, M. R.; Draghici, C.; Barbu, L. *Anal. Sci. X* **2005**, *21*, x133; doi: 10.2116/analscix.21.x133. (h) Butler, R. N.; Coyne, A. G.; Moloney, E. M. *Tetrahedron Lett.* **2007**, *48*, 3501.

(5) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, **2005**. (c) Olimpieria, F.; Volonterio, A.; Zanda, M. *Synlett* **2008**, 3016. (d) Barthelon, A.; Legoff, X.-F.; El-Kaim, L.; Grimaud, L. *Synlett* **2010**, 153. (e) Kantevari, S.; Yempala, T.; Vuppalapati, S. V. N. *Synthesis* **2010**, 959. (f) Gan, S.-F.; Wan, J.-P.; Pan, Y.-J.; Sun, C.-R. *Synlett* **2010**, 973. (g) Willy, B.; Müller, T. J. J. *ARKIVOC* **2008**, *(i)*, 195. (h) Esmaeili, A. A.; Hosseinabadi, R.; Habibi, A. *Synlett* **2010**, 1477. (i) Kobayashi, K.; Fujita, S.; Fukamachi, S.; Konishi, H. *Synthesis* **2009**, 3378. (j) Alizadeh, A.; Noaparast, Z.; Sabahnoo, H.; Zohreh, N. *Synlett* **2010**, 1469. (k) Zhao, K.; Xu, X.-P.; Zhu, S.-L.; Shi, D.-Q.; Zhang, Y.; Ji, S.-J. *Synthesis* **2009**, 2697. (l) Maisonneuve, S.; Xie, J. *Synlett* **2009**, 2977. (m) Zhang, W.; Kuang, C.; Yang, Q. *Synthesis* **2010**, 283. (n) Reddy Udagandla, C.; Saikia Anil, K. *Synlett* **2010**, 1027.

(6) (a) Dumitrascu, F.; Caira, M. R.; Draghici, B.; Caproiu, M. T.; Dumitrescu, D. G. *Synlett* **2008**, 813. (b) Vasilescu, M.; Bandula, R.; Cramariuc, O.; Hukka, T.; Lemmetyinen, H.; Rantala, T. T.; Dumitrascu, F. *J. Photochem. Photobiol., A* **2008**, *194*, 308. (c) Georgescu, E.; Caira, M. R.; Georgescu, F.; Draghici, B.; Popa, M. M.; Dumitrascu, F. *Synlett* **2009**, 1795. (d) Caira, M. R.; Georgescu, E.; Georgescu, F.; Draghici, B.; Popa, M. M.; Dumitrascu, F. *ARKIVOC* **2009**, *(xii)*, 242. (e) Dumitrascu, F.; Georgescu, E.; Caira, M. R.; Georgescu, F.; Popa, M.; Draghici, B.; Dumitrescu, D. G. *Synlett* **2009**, 3336. (f) Georgescu, E.; Dumitrascu, F.; Georgescu, F.; Draghici, C.; Popa, M. M. *Rev. Roum. Chim.* **2010**, *55*, 217.

(7) **General Procedure for the Synthesis of Pyrrolo[2,1-*a*]phthalazines 4**: Phthalazine **1** (5 mmol), phenacyl bromide **2** (5 mmol)and nonsymmetrical acetylene **3** (5 mmol; methyl propiolate, ethyl propiolate, 3-butyn-2-one) in 1,2-epoxybutane (20 mL) were refluxed with stirring for 12 h. The solvent was partly removed by evaporation, MeOH (10 mL) was added and the mixture was left overnight at r.t. The solid was filtered, washed with a small quantity of cold EtOH and crystallized from a suitable solvent. **3-Acetyl-1-(4-methoxybenzoyl)pyrrolo[2,1-*a*]phthalazine (4c)**: colorless crystals with mp 158–160 °C were obtained by recrystallization from MeOH. Yield: 71%. Anal. Calcd $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.51; H, 4.97; N, 8.38. ATR-IR: 1089, 1256, 1659, 1672, 2986, 3050 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.68 (s, 3 H, MeCO), 3.90 (s, 3 H, OMe), 7.00 (d, 2 H, *J* = 9.0 Hz, H-3′, H-5′), 7.60 (s, 1 H, H-2), 7.71–7.76 (m, 1 H, H-8), 7.85–7.91 (m, 2 H, H-7, H-9), 7.97 (d, 2 H, *J* = 9.0 Hz, H-2′, H-6′), 8.72 (d, 1 H, *J* = 0.8 Hz, H-6), 9.82–9.85 (m, 1 H, H-10). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 29.7 (MeCO), 55.7 (OMe), 113.9 (C-3′, C-5′), 117.0 (C-1), 123.5 (C-2), 127.6, 127.7 (C-7, C-10), 122.3, 127.3, 129.2, 131.5 (C-3, C-6a, C-10a, C-10b), 130.0 (C-8), 132.3 (C-2′, C-6′), 132.9 (C-9), 132.9 (C-1′), 146.9 (C-6), 163.5 (C-4′), 183.7 (COAr), 193.8 (COMe).

(8) **General Procedure for the Synthesis of Pyrrolo[2,1-*a*]phthalazines 5; Method A**: Phthalazine **1** (5 mmol)and phenacyl bromide **2** (5 mmol) were stirred for 30 min in 1,2-epoxybutane (20 mL) and then acetylenic dipolarophile (DMAD, DEAD, DIPAD; 7 mmol) was added and the reaction was kept under reflux for 12 h. The solvent was partly removed by evaporation, MeOH (10 mL) was added and the mixture was left overnight at r.t. The solid was filtered, washed on a filter with cold EtOH and crystallized

from a suitable solvent. **Method B**: Phthalazinium bromide **2** (5 mmol) and symmetrical acetylenic dipolarophile **3** (7 mmol) in 1,2-epoxybutane (20 mL) were refluxed for 24 h. The workup of the reaction mixture was similar to method A. **Diethyl 1-(4-Chlorobenzoyl)pyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (5h)**: colorless crystals with mp 153–154 °C were obtained by recrystallization from MeOH. Yield: 77%. Anal. Calcd $C_{24}H_{19}ClN_2O_5$: C, 63.93; H, 4.25; Cl, 7.86; N, 6.21. Found: C, 64.27; H, 4.61; Cl, 8.19; N, 6.01. ATR-IR: 1086, 1234, 1682, 1694, 1725, 2956, 3036 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, 3 H, *J* = 7.1 Hz, Me), 1.40 (t, 3 H, *J* = 7.1 Hz, Me), 4.10 (q, 2 H, *J* = 7.1 Hz, $CH_2$), 4.47 (q, 2 H, *J* = 7.1 Hz, $CH_2$), 7.42 (d, 2 H, *J* = 8.6 Hz, H-3′, H-5′), 7.62–7.67 (m, 1 H, H-8), 7.77–7.84 (m, 2 H, H-7, H-9), 7.81 (d, 2 H, *J* = 8.9 Hz, H-2′, H-6′), 8.45 (s, 1 H, H-6), 8.90–8.93 (m, 1 H, H-10). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.6, 14.0 (2 × Me), 61.3, 62.7 (2 × $CH_2$), 108.0 (C-1), 119.5, 121.1, 124.4, 126.6, 128.0 (C-2, C-3, C-6a, C-10a, C-10b), 124.5 (C-10), 128.2, 133.4 (C-7, C-9), 128.8 (C-3′, C-5′), 129.0 (C-8), 130.1 (C-2′, C-6′), 136.0 (C-4′), 140.6 (C-1′), 147.0 (C-6), 163.2, 165.2 (2 × COO), 185.8 (COAr).

(9) Huntress, E. H.; Lesslie, T. E.; Bornstein, J. *Org. Synth., Coll. Vol. IV*; John Wiley & Sons: London, **1963**, 329.
(10) (a) Zugrăvescu, I.; Petrovanu, M. *N-Ylid Chemistry*; McGraw-Hill: New York, **1976**, 239. (b) Caprosu, M. C.; Zbancioc, G. N.; Moldoveanu, C. C.; Mangalagiu, I. *Collect. Czech. Chem. Commun.* **2004**, *69*, 426.
(11) (a) Wei, X.; Hu, Y.; Li, T.; Hu, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2487. (b) Wang, B.; Hu, J.; Zhang, X.; Hu, Y.; Hu, H. *J. Heterocycl. Chem.* **2000**, *37*, 1533. (c) Zhou, J.; Hu, Y.; Hu, H. *J. Heterocycl. Chem.* **2000**, *37*, 1165. (d) Dumitrascu, F.; Draghici, C.; Miu, B.; Caproiu, M. T.; Barbu, L.; Dumitrescu, D. G. *Rev. Roum. Chim.* **2008**, *53*, 261.