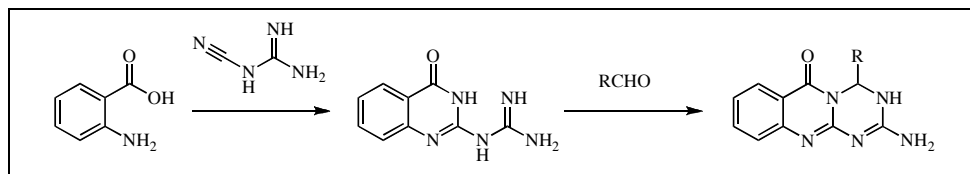


Anton V. Dolzhenko,* Anna V. Dolzhenko and Wai-Keung Chui

Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore. E-mail phada@nus.edu.sg

Received May 10, 2007



The 2-amino-4-(het)aryl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-ones were prepared readily by cyclocondensation of anthranilic acid derived 4-oxo-3,4-dihydroquinazolinyl-2-guanidine with a variety of aldehydes. The structures of the compounds were confirmed by nmr spectroscopy, including 2D NOESY experiments.

J. Heterocyclic Chem., **45**, 173 (2008).

INTRODUCTION

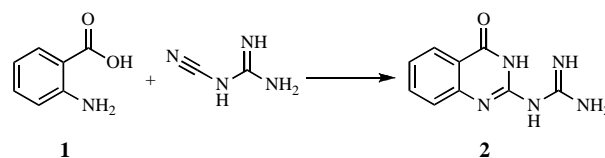
Naturally occurring and synthetic quinazolinone derivatives, including fused systems, are known to possess a wide range of biological activities [2-4]. Three isomeric structures are possible for quinazoline fused with 1,3,5-triazine nucleus, *viz.* 1,3,5-triazino[1,2-*a*]quinazoline, 1,3,5-triazino[1,2-*c*]quinazoline and 1,3,5-triazino[2,1-*b*]quinazoline heterocyclic systems. The known methods of the synthesis of these compounds are limited. The system with [1,2-*a*] ring junction has been prepared *via* (2+2+2) cycloaddition of two isocyanate molecules to the side 'a' of quinazolines [5,6] or by (3+3) heterocyclization of 2-aminoquinazolines with chlorocarbonyl isocyanate [7]. The annulation of 1,3,5-triazine ring onto the side 'c' of the quinazolines with the formation of 1,3,5-triazino[1,2-*c*]quinazolines was also reported [8-11].

Among the methods of 1,3,5-triazino[2,1-*b*]quinazolines synthesis [8,12-14], only one annulation of 1,3,5-triazine ring onto an existing quinazoline skeleton has been reported [8] using thermal ring closure of 2-benzamido-3-cyano-3,4-dihydroquinazolin-4-one. As a continuation of our investigations [1,15-18] of fused 1,3,5-triazines syntheses *via* the reactions of hetarylguanidines with aldehydes, we describe herein the reaction of 4-oxo-3,4-dihydroquinazolinyl-2-guanidines with benzaldehydes and hetarylaldehydes.

RESULTS AND DISCUSSION

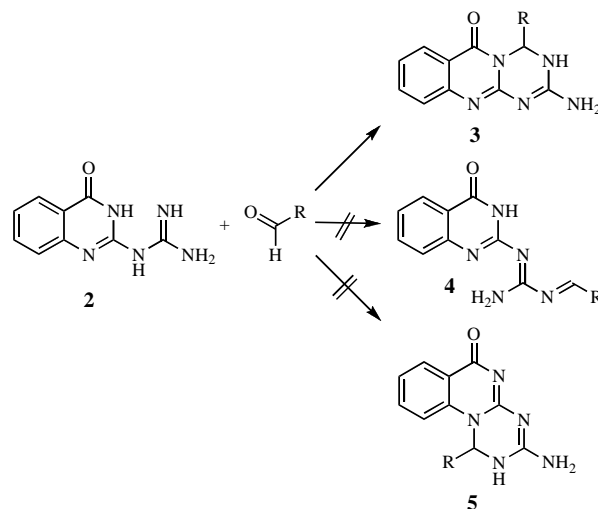
The 4-oxo-3,4-dihydroquinazolinyl-2-guanidine (2) was prepared by cyclocondensation of anthranilic acid (1) with cyanoguanidine (Scheme 1) using the reported method [19].

Scheme 1



The reaction of 4-oxo-3,4-dihydroquinazolinyl-2-guanidine (2) with aldehydes in DMF proceeded *via* (5+1) heterocyclization and resulted in the formation of hitherto unknown 2-amino-4-(het)aryl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-ones (3) (Scheme 2).

Scheme 2

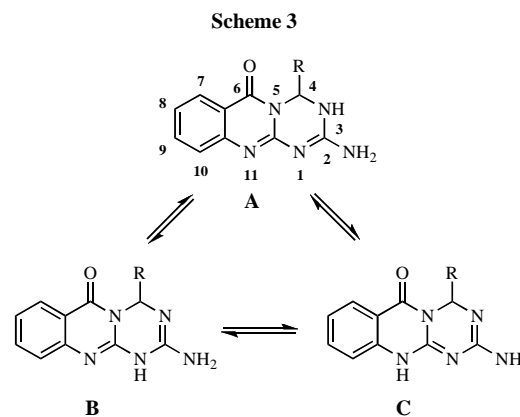


The structures of the products were established using data of nmr and ir spectroscopy. The formation of the dihydro-*s*-triazine ring in the reaction was suggested by the singlet of H-4 observed at 6.90-7.04 ppm in the ¹H

nmr spectra of **3**, together with the signal of C-4 at 60.4–61.0 ppm in the ^{13}C nmr spectra. This strong evidence of the sp^3 hybridization of C-4 ruled out the structure of the possible Schiff base-like compounds **4**. The alternative structure **5** might arise in case of the ring closure to the side 'a' of the quinazolone. The carbonyl group $\text{C}=\text{O}$ vibrations in ir spectra of the compounds obtained were observed at a considerably lower frequency compared to $\text{C}=\text{O}$ signal of **2**. These results indicated that the nitrogen atom adjacent to the $\text{C}=\text{O}$ group might be involved in the ring closure. The 1,3,5-triazino[1,2-*a*]quinazolines (**5**) would show in 2D NOESY nmr experiments cross-peaks between the singlet of proton located at sp^3 hybridized carbon atom and one of the doublets of the phenylene part of the molecule. As there were no cross-peaks found for these signals, the structure of 1,3,5-triazino[2,1-*b*]quinazolines (**3**) was assigned for the prepared compounds.

Annular prototropic tautomerism was observed in dimethyl sulfoxide solution for compounds **3** (*viz.* 1*H*-, 3*H*- and 11*H*- tautomeric forms) (Scheme 3).

The prototropic interconversion between these tautomeric forms was postulated based on the broadening of the several signals of 4,6-dihydro-1(3)(11)*H*-[1,3,5]-triazino[2,1-*b*]quinazolin-6-one heterocyclic system in the ^{13}C nmr spectra of compounds **3**. The pattern of the broadening of signals indicated that all the three forms (**A**, **B** and **C**) were involved in the proton transfer. The broadening of C-4 signal referred to **A-B** equilibrium and the broad signals of C-10a indicated **B-C** interconversion. At the same time, the broadening of C-10a signals also confirmed the structure **3**, since in the alternative structure **5** this phenylene carbon atom would not be in close proximity with the nitrogen atoms involved in the tautomerization.



In conclusion, we developed a simple method for the fusion of the 1,3,5-triazine ring to the side 'b' of quinazolines with the formation of 2-amino-4-(het)aryl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-ones.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. Nmr spectra were recorded on a Bruker DPX-300 spectrometer, using dimethyl sulfoxide- d_6 as a solvent and TMS as an internal reference. The assignments were made using 2D COSY, NOESY and HMQC experiments. Ir spectra were performed on a Jasco FT-IR-430 spectrophotometer in potassium bromide pellets. The course of the reactions was monitored by tlc on Silica gel 60 F_{254} plates (Merck, Germany).

Preparation of 4-oxo-3,4-dihydroquinazolinyl-2-guanidine (2). Anthranilic acid (**1**) (6.9 g, 50 mmole) was dissolved on heating in 50 mL of 10% sulfuric acid and cyanoguanidine (6.3 g, 75 mmole) was added. The reaction mixture was heated for 20 min and then 10 mL of 50% sodium hydroxide solution was

Table 1
2-Amino-4-(het)aryl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-ones

Compound	R	Mp (°C)	Yield %	Molecular Formula	Analysis %, Calcd./Found		
					C	H	N
3a	Ph	302-303	61	$\text{C}_{16}\text{H}_{13}\text{N}_5\text{O}$	65.97	4.50	24.04
					65.63	4.72	23.89
3b	$\text{C}_6\text{H}_4\text{Me-4}$	248-251	52	$\text{C}_{17}\text{H}_{15}\text{N}_5\text{O}$	66.87	4.95	22.94
					66.58	4.90	22.87
3c	$\text{C}_6\text{H}_4\text{OMe-4}$	246-248	55	$\text{C}_{17}\text{H}_{15}\text{N}_5\text{O}_2$	63.54	4.71	21.79
					63.09	4.83	21.62
3d	$\text{C}_6\text{H}_4\text{F-4}$	257-258	62	$\text{C}_{16}\text{H}_{12}\text{FN}_5\text{O}$	62.13	3.91	22.64
					61.86	4.18	22.45
3e	$\text{C}_6\text{H}_4\text{Cl-4}$	263-264	63	$\text{C}_{16}\text{H}_{12}\text{ClN}_5\text{O}$	58.99	3.71	21.50
					58.72	4.03	21.37
3f	$\text{C}_6\text{H}_4\text{Br-4}$	267-269	74	$\text{C}_{16}\text{H}_{12}\text{BrN}_5\text{O}$	51.91	3.27	18.92
					51.60	3.52	18.67
3g	Furyl-2	280	60	$\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}_2$	59.78	3.94	24.90
					59.41	4.23	24.65
3h	Thienyl-2	297	58	$\text{C}_{14}\text{H}_{11}\text{N}_5\text{OS}$	56.55	3.73	23.55
					56.17	3.36	23.42
3i	Pyridyl-3	285-286	82	$\text{C}_{15}\text{H}_{12}\text{N}_6\text{O}$	61.64	4.14	28.75
					61.30	4.02	28.55

Table 2

Spectral Data of 2-Amino-4-(het)aryl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-ones

Compound	ir, potassium bromide, ν (cm ⁻¹)	¹ H nmr (300 MHz) dimethyl sulfoxide- <i>d</i> ₆ /TMS, δ (ppm)	¹³ C nmr (75 MHz) dimethyl sulfoxide- <i>d</i> ₆ /TMS, δ (ppm)
3a	NH 3464, NH 3331, CH 3069, C=O 1680, 1654, 1613, 1575, 1527, 1468, 1417, 1272, 764, 694	6.98 (br s, 2H, NH ₂), 7.00 (s, 1H, H-4), 7.17 (t, <i>J</i> = 7.5 Hz, 1H, H-8), 7.24-7.40 (m, 6H, H-10 and Ph), 7.62 (td, <i>J</i> = 7.7, 1.5 Hz, 1H, H-9), 7.94 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H, H-7), 8.32 (s, 1H, NH)	60.9 (br s, C-4), 117.7 (C-6a), 122.4 (C-8), 125.3 (C-10), 125.5 (C-2' and -6'), 126.2 (C-7), 128.4 (C-3' and -5'), 128.6 (C-4'), 134.2 (C-9), 140.2 (C-1'), 149.9 (br s, C-10a), 150.5 (br s, C-11a), 156.8 (br s, C-2), 160.4 (C-6)
3b	NH 3446, NH 3329, CH 3061, C=O 1683, 1655, 1611, 1573, 1527, 1467, 1417, 1267, 774, 694	2.24 (s, 3H, Me), 6.97 (s, 1H, H-4), 7.03 (br s, 2H, NH ₂), 7.10-7.23 (m, 5H, H-8, -2', -3', -5' and -6'), 7.32 (d, <i>J</i> = 7.9 Hz, 1H, H-10), 7.62 (t, <i>J</i> = 7.5 Hz, 1H, H-9), 7.94 (d, <i>J</i> = 7.9 Hz, 1H, H-7), 8.42 (br s, 1H, NH)	20.5 (Me), 61.0 (br s, C-4), 117.7 (C-6a), 122.4 (C-8), 125.2 (C-10, -2' and -6'), 126.2 (C-7), 129.1 (C-3' and -5'), 134.2 (C-9), 137.3 (C-1'), 137.8 (C-4'), 149.8 (br s, C-10a), 150.2 (br s, C-11a), 156.6 (br s, C-2), 160.3 (C-6)
3c	NH 3463, NH 3341, CH 3070, C=O 1676, 1656, 1611, 1574, 1514, 1467, 1421, 1268, 1257, 1176, 1031, 761, 694	3.70 (s, 3H, OMe), 6.90 (d, <i>J</i> = 8.7 Hz, 2H, H-2' and -6'), 6.95 (s, 1H, H-4), 6.97 (br s, 2H, NH ₂), 7.16 (t, <i>J</i> = 7.5 Hz, 1H, H-8), 7.21 (d, <i>J</i> = 8.7 Hz, 2H, H-3' and -5'), 7.31 (d, <i>J</i> = 8.3 Hz, 1H, H-10), 7.61 (t, <i>J</i> = 7.5 Hz, 1H, H-9), 7.93 (d, <i>J</i> = 7.9 Hz, 1H, H-7), 8.26 (br s, 1H, NH)	55.0 (OMe), 60.6 (br s, C-4), 113.9 (C-3' and -5'), 117.7 (C-6a), 122.3 (C-8), 125.4 (C-10), 126.2 (C-7), 126.7 (C-2' and -6'), 132.4 (C-1'), 134.2 (C-9), 149.8 (br s, C-10a), 150.4 (br s, C-11a), 156.9 (br s, C-2), 159.2 (C-4'), 160.3 (C-6)
3d	NH 3457, NH 3332, CH 3070, C=O 1683, 1654, 1604, 1575, 1528, 1467, 1414, 1268, CF 1236, 765, 693	7.00 (s, 1H, H-4), 7.01 (br s, 2H, NH ₂), 7.18 (t, <i>J</i> = 7.2 Hz, 1H, H-8), 7.20 (dd, <i>J</i> = 8.5 Hz, ³ <i>J</i> _{HF} = 8.5 Hz, 2H, H-3' and -5'), 7.27-7.38 (m, 3H, H-10, -2' and -6'), 7.63 (td, <i>J</i> = 7.9, 1.1 Hz, 1H, H-9), 7.94 (dd, <i>J</i> = 7.9, 1.1 Hz, 1H, H-7), 8.30 (s, 1H, NH)	60.4 (br s, C-4), 115.5 (d, ² <i>J</i> _{CF} = 21.8 Hz, C-3' and -5'), 117.7 (C-6a), 122.4 (C-8), 125.5 (C-10), 126.2 (C-7), 127.5 (d, ³ <i>J</i> _{CF} = 8.2 Hz, C-2' and -6'), 134.3 (C-9), 136.6 (d, ⁴ <i>J</i> _{CF} = 2.4 Hz, C-1'), 149.7 (br s, C-10a), 150.5 (br s, C-11a), 156.8 (br s, C-2), 160.4 (C-6), 161.9 (d, ¹ <i>J</i> _{CF} = 244.6 Hz, C-4')
3e	NH 3458, NH 3336, CH 3065, C=O 1680, 1653, 1611, 1573, 1531, 1466, 1414, 1270, CCl 1093, 772, 759	7.01 (s, 1H, H-4), 7.02 (br s, 2H, NH ₂), 7.18 (t, <i>J</i> = 7.5 Hz, 1H, H-8), 7.29 (d, <i>J</i> = 8.3 Hz, 2H, H-2' and -6'), 7.32 (d, <i>J</i> = 7.9 Hz, 1H, H-10), 7.44 (d, <i>J</i> = 8.3 Hz, 2H, H-3' and -5'), 7.63 (t, <i>J</i> = 7.5 Hz, 1H, H-9), 7.94 (d, <i>J</i> = 7.9 Hz, 1H, H-7), 8.32 (br s, 1H, NH)	60.4 (br s, C-4), 117.7 (C-6a), 122.5 (C-8), 125.5 (C-10), 126.2 (C-7), 127.3 (C-2' and -6'), 128.7 (C-3' and -5'), 133.1 (C-4'), 134.3 (C-9), 139.2 (C-1'), 149.6 (br s, C-10a), 150.4 (br s, C-11a), 156.8 (br s, C-2), 160.4 (C-6)
3f	3458 (NH, st), 3339 (NH, st), 3064 (CH, m), 1683 (C=O, st), 1651, 1611, 1577, 1530, 1467, 1423, 1270, 1011 (CBr, st), 771, 761	6.99 (s, 1H, H-4), 7.04 (br s, 2H, NH ₂), 7.18 (t, <i>J</i> = 7.7 Hz, 1H, H-8), 7.22 (d, <i>J</i> = 8.3 Hz, 2H, H-2' and -6'), 7.33 (d, <i>J</i> = 7.9 Hz, 1H, H-10), 7.58 (d, <i>J</i> = 8.3 Hz, 2H, H-3' and -5'), 7.63 (t, <i>J</i> = 7.9 Hz, 1H, H-9), 7.94 (d, <i>J</i> = 7.9 Hz, 1H, H-7), 8.31 (br s, 1H, NH)	60.5 (br s, C-4), 117.6 (C-6a), 121.6 (C-4'), 122.4 (C-8), 125.5 (C-10), 126.2 (C-7), 127.6 (C-2' and -6'), 131.6 (C-3' and -5'), 134.3 (C-9), 139.6 (C-1'), 149.6 (br s, C-10a), 150.4 (br s, C-11a), 156.7 (br s, C-2), 160.4 (C-6)
3g	NH 3451, CH 3020, C=O 1681, 1651, 1632, 1611, 1578, 1520, 1469, 1417, 1271, 1011, 799, 769	6.28 (d, <i>J</i> = 3.0 Hz, 1H, H-3'), 6.40 (dd, <i>J</i> = 3.0, 1.5 Hz, 1H, H-4'), 7.05 (s, 1H, H-4), 7.06 (br s, 2H, NH ₂), 7.19 (t, <i>J</i> = 7.3 Hz, 1H, H-8), 7.32 (d, <i>J</i> = 7.9 Hz, 1H, H-10), 7.60 (d, <i>J</i> = 1.5 Hz, 1H, H-5'), 7.63 (t, <i>J</i> = 7.5 Hz, 1H, H-9), 7.95 (d, <i>J</i> = 7.9 Hz, 1H, H-7), 8.32 (1H, s, NH)	56.1 (br s, C-4), 107.2 (C-3'), 110.4 (C-4'), 117.7 (C-6a), 122.5 (C-8), 125.4 (C-10), 126.2 (C-7), 134.3 (C-9), 143.1 (C-5'), 149.2 (br s, C-10a), 150.2 (br s, C-11a), 151.6 (C-2'), 156.7 (br s, C-2), 159.9 (C-6)
3h	NH 3466, CH 3020, C=O 1679, 1651, 1628, 1610, 1570, 1533, 1518, 1468, 1414, 1271, 768, 702	6.96 (dd, <i>J</i> = 4.9, 3.5 Hz, 1H, H-4'), 7.04 (d, <i>J</i> = 3.5 Hz, 1H, H-3'), 7.14 (br s, 2H, NH ₂), 7.19 (t, <i>J</i> = 7.5 Hz, 1H, H-8), 7.24 (s, 1H, H-4), 7.31 (d, <i>J</i> = 8.3 Hz, 1H, H-10), 7.44 (d, <i>J</i> = 4.9 Hz, 1H, H-5'), 7.62 (t, <i>J</i> = 7.5 Hz, 1H, H-9), 7.97 (d, <i>J</i> = 7.9 Hz, 1H, H-7), 8.36 (s, 1H, NH)	57.8 (br s, C-4), 117.7 (C-6a), 122.4 (C-8), 125.2 (C-3'), 125.5 (C-10), 126.2 (C-7 and -5'), 126.4 (C-4'), 134.3 (C-9), 143.1 (C-2'), 149.1 (br s, C-10a), 150.4 (br s, C-11a), 156.9 (br s, C-2), 160.1 (C-6)
3i	NH 3363, NH 3327, CH 3060, C=O 1683, 1671, 1607, 1582, 1527, 1471, 1416, 1270, 1025, 764	7.08 (s, 1H, H-4), 7.09 (br s, 2H, NH ₂), 7.20 (t, <i>J</i> = 7.3 Hz, 1H, H-8), 7.34 (d, <i>J</i> = 7.9 Hz, 1H, H-10), 7.40 (dd, <i>J</i> = 7.9, 4.9 Hz, 1H, H-5'), 7.62 (dd, <i>J</i> = 7.9, 1.8 Hz, 1H, H-6'), 7.64 (td, <i>J</i> = 8.1, 0.8 Hz, 1H, H-9), 7.95 (dd, <i>J</i> = 7.9, 0.8 Hz, 1H, H-7), 8.36 (s, 1H, NH), 8.54 (dd, <i>J</i> = 4.9, 1.5 Hz, 1H, H-4'), 8.56 (d, <i>J</i> = 2.3 Hz, 1H, H-2')	59.5 (br s, C-4), 117.6 (C-6a), 122.6 (C-8), 123.8 (C-5'), 125.5 (C-10), 126.2 (C-7), 133.0 (C-4'), 134.4 (C-9), 135.8 (C-3'), 147.0 (C-2'), 149.6 (br s, C-10a), 149.7 (C-6'), 150.4 (br s, C-11a), 156.8 (br s, C-2), 160.4 (C-6)

added. After heating for additional 15 min, the reaction mixture was cooled, the solid collected by filtration and washed with water. The prepared compound was sufficiently pure and was used without further purification. After recrystallization from 5% sodium hydroxide solution mp of the product (**2**) did not change and was 317 °C (lit. [19] mp 316-

317 °C); yield 70%; ¹H nmr (300 MHz) dimethyl sulfoxide-*d*₆/TMS, δ (ppm): 7.18 (t, *J* = 7.3 Hz, 1H, H-6), 7.37 (d, *J* = 7.9 Hz, 1H, H-8), 7.60 (t, *J* = 7.5 Hz, 1H, H-7), 7.83 (br s, 4H, NH-C(=NH)NH₂), 7.95 (d, *J* = 7.9 Hz, 1H, H-5), 11.37 (br s, 1H, N(3)H); ¹³C nmr (75 MHz) dimethyl sulfoxide-*d*₆/TMS, δ (ppm): 118.1 (C-4a), 122.3 (C-6), 124.2 (br s, C-8), 125.7 (C-

5), 133.5 (C-7), 149.2 (br s, C-8a), 156.1 (C-2), 159.4 (NH-C(=NH)NH₂), 165.4 (C=O); ir (potassium bromide): NH 3402, NH 3340, CH 3048, C=O 1702, 1669, 1624, 1585, 1502, 1456, 1315, 767 cm⁻¹.

General Procedure for the Synthesis of 2-Amino-4-(het)aryl-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinoxalin-6-ones (3). A mixture of 4-oxo-3,4-dihydroquinazolinyl-2-guanidine (2) (0.51 g, 2.5 mmole) and appropriate arylaldehyde (5.0 mmole) in DMF (5 mL) was heated under reflux for 2-10 h and concentrated under vacuum. The product (3) was filtered, washed with ethanol and recrystallized from DMF.

Acknowledgement. This work is supported by the Academic Research Fund (WBS R-148-000-069-112) from the National University of Singapore.

REFERENCES

- [1] Part 9 in the series "Fused heterocyclic systems with s-triazine ring", for part 8 see Dolzhenko, A. V.; Dolzhenko, A. V.; Chui, W. K. *Tetrahedron*, in press.
- [2] Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787.
- [3] El-Hiti, G. A.; Abdel-Megeed, M. F. *Heterocycles* **2005**, *65*, 3007.
- [4] Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153.
- [5] Sawada, M.; Furukawa, Y.; Takai, Y.; Hanafusa, T. *Heterocycles* **1984**, *22*, 501.
- [6] Tietz, H.; Rademacher, O.; Zahn, G. *Eur. J. Org. Chem.* **2000**, 2105.
- [7] Kamal, A.; Sattur, P. B. *Synthesis* **1985**, 892.
- [8] Shaw, J. T.; Taylor, D. M.; Corbett, F. J.; Ballentine, J. D. *J. Heterocycl. Chem.* **1972**, *9*, 125.
- [9] Abdel-Megeed, M. F.; Teniou, A. *Collect. Czech. Chem. Commun.* **1988**, *53*, 329.
- [10] Aly, A. A. M. *J. Chem. Res.* **2006**, 461.
- [11] Aly, A. A. *Z. Naturforsch.* **2006**, *61B*, 1012.
- [12] Shaw, J. T.; Ballentine, J. *J. Chem. Soc., D. Chem. Commun.* **1969**, 1040.
- [13] Winter, R. A. E.; Villani, T. J. United State Patent 3,887,554, 1975; *Chem. Abstr.* **1975**, *83*, 147505.
- [14] Balli, H.; Gunzenhauser, S.; Fletcher, I. J.; Bedekovic, D. German Patent 3,314,195, 1983; *Chem. Abstr.* **1984**, *100*, 87256.
- [15] Dolzhenko, A. V.; Chui, W. K.; Dolzhenko, A. V.; Chan, L. *W. J. Fluorine Chem.* **2005**, *126*, 759.
- [16] Dolzhenko, A. V.; Chui, W. K. *J. Heterocycl. Chem.* **2006**, *43*, 95.
- [17] Dolzhenko, A. V.; Chui, W. K.; Dolzhenko, A. V. *J. Heterocycl. Chem.* **2006**, *43*, 1513.
- [18] Dolzhenko, A. V.; Tan, G. K.; Koh, L. L.; Dolzhenko, A. V.; Chui, W. K. *Acta Crystallogr.* **2007**, *E63*, o2796.
- [19] Skowronska-Serafinowa, B.; Urbanski, T. *Rocz. Chem.* **1952**, *26*, 51.