1,2,3-Triazolo[4,5-*e*]-1,2,4-Triazolo[3,4-*c*]pyrimidines

Giuliana Biagi, Irene Giorgi, Oreste Livi*, Clementina Manera, and Valerio Scartoni

Dipartimento di Scienze Farmaceutiche, Facoltà di Farmacia,
Università di Pisa, via Bonanno 6, 56126 Pisa, Italy

Received April 26, 1999

Some new 1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidines were prepared starting from the corresponding 1,2,3-triazolo[4,5-*d*]pyrimidines *via* the formation of the 1,2,4-triazole ring. Thus suitable hydrazino derivatives **6** were condensed with triethyl orthoformate, triethyl orthoacetate and triethyl orthobenzoate to give the expected tricyclic derivatives **7, 8** and **9**. Intramolecular cyclization of the ethoxycarbonylhydrazino derivatives **10** gave the tricyclic compounds **11** bearing an hydroxyl group in the 3 position. The *v*-triazolo-*s*-triazolopyrimidine derivatives were tested towards the A_1 and A_{2A} adenosine receptors in binding assays, but they did not show any receptor affinity.

J. Heterocyclic Chem., **36**, 1195 (1999).

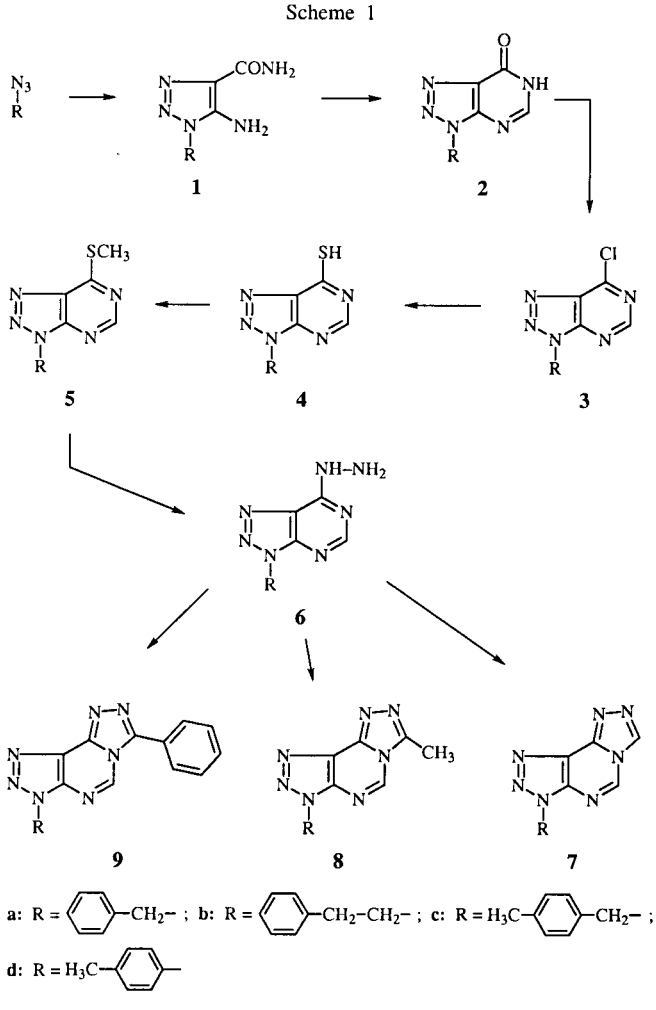
The 1-benzoyloxy-7-phenyl-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidine derivative was mentioned in a short paper published in 1978, concerning the thermolysis of *N*-hetaryltetrazoles with the generation of nitrilimines to give competitive intramolecular 1,x-dipolar cyclizations [1]. In 1990, while pursuing the synthesis of novel nitrogen-rich heterocycles, Ried and Laoutidis [2] obtained some *v*-triazolo-*s*-triazolopyrimidine derivatives by the cyclization of 7-hydrazino-1*H*-1,2,3-triazolo[4,5-*d*]pyrimidines with triethyl orthoformate or triethyl orthoacetate.

Italian authors [3,4,5] have patented derivatives with the isomeric structure 1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo-[1,5-*c*]pyrimidine (together with analogous derivatives with a pyrazolo or imidazole ring in place of the 1,2,3-triazole), which show a high, selective antagonistic activity towards A_{2A}-adenosine receptors. However, the 1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidine derivatives have not been studied in detail, and the biological properties of this tricyclic structure, which can also be correlated to other similar pharmacologically active tricyclic structures [6,7], are practically unknown. For these reasons, after studying the isomeric *v*-triazolo-5-triazolopyridazine structure [8], we followed an analogous synthetic route using the 1,2,3-triazolo[4,5-*d*]pyrimidine compounds which had been the subject of our studies [9], in order to prepare 1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]-pyrimidines bearing lipophilic substituents in the 3 position of the heterocyclic ring.

This synthesis was based upon the formation of the 1,2,4-triazole ring by condensation of an appropriate monocarbon fragment with the 4-hydrazino substituent, with the nitrogen atom in the 6 position of the 1,2,3-triazolo[4,5-*d*]pyrimidine ring [2].

The reaction sequence followed for the synthesis of the tricyclic derivatives is illustrated in Scheme 1: by cycloaddition of the appropriate azide {benzyl azide [10] (series a), phenethyl azide [11] (series b), *p*-methylbenzyl azide [12] (series c) and *p*-methylphenyl azide [13] (series d)} to cyanacetamide in ethanol/sodium ethoxide, the corresponding triazole derivatives **1a-d** were obtained, which were easily converted into the relative

Scheme 1



3-substituted-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyrimidine derivatives **2a-d** by heating in formamide. Chlorination of compounds **2a-d** with thionyl chloride in chloroform/dimethylformamide provided the 7-chloro derivatives **3a-d** in 50-70% yields. The direct reaction of the chloro derivative **3a** with 99% hydrazine hydrate or partially anhydrified hydrazine gave the corresponding hydrazino

Table I

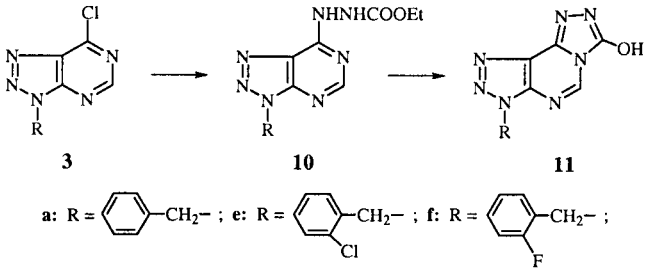
Chemical and Physical Properties of Derivatives **1-11**

Compound	Yield %	Crystall. Solvent	Mp °C	Mass m/z M +	Mass m/z base peak	Elemental Analysis	Calcd./Found C	H	N
1c	83	EtOH	218-222			$C_{11}H_{13}N_5O$	57.13 57.14	5.67 5.63	30.28 30.30
2b	89	EtOH	262-264	241	150	$C_{12}H_{10}N_5O$	59.99 59.61	4.20 4.49	29.15 28.81
2c	94	EtOH	257-259	241	184	$C_{12}H_{10}N_5O$	59.99 59.72	4.20 4.47	29.15 28.80
3b	76	60-80° petroleum ether	94-96	259	104	$C_{12}H_{10}N_5Cl$	55.50 55.56	3.88 3.92	26.97 27.28
3c	45	60-80° petroleum ether	88-91	259	105	$C_{12}H_{10}N_5Cl$	55.50 55.45	3.88 3.99	26.97 26.61
4b	97	-----	167-170	257	104	$C_{12}H_{11}N_5S$	56.01 55.62	4.31 4.35	27.22 27.15
4c	98	-----	205-207	257	105	$C_{12}H_{11}N_5S$	56.01 56.37	4.31 4.36	27.22 27.50
4d	95	-----	186-188	244	91	$C_{11}H_{10}N_5S$	54.08 53.98	4.13 3.76	28.67 28.81
5b	95	-----	62-63	271	79	$C_{13}H_{13}N_5S$	57.55 57.60	4.83 4.82	25.83 25.83
5c	92	-----	119-121	271	105	$C_{13}H_{13}N_5S$	57.55 57.20	4.83 4.75	25.83 25.51
5d	99	EtOH	129-131	259	91	$C_{12}H_{13}N_5S$	55.58 55.68	5.05 4.70	27.01 27.22
6b	77	MeOH	155-158	255	151	$C_{12}H_{13}N_7$	56.46 56.20	5.13 4.75	38.41 38.43
6c	88	MeOH	209-212	255	105	$C_{12}H_{13}N_7$	56.46 56.49	5.13 5.10	38.41 38.34
6d	86	MeOH	194-195	241	91	$C_{11}H_{11}N_7$	54.76 54.42	4.60 4.55	40.64 40.24
7b	63	EtOH	198-200	265	174	$C_{13}H_{11}N_7$	58.86 58.85	4.18 4.37	36.96 37.30
7c	77	EtOH	226-229	265	105	$C_{13}H_{11}N_7$	58.86 58.46	4.18 4.37	36.96 36.81
7d	64	EtOH	213-216	251	222	$C_{12}H_9N_7$	57.37 57.62	3.61 3.65	39.02 39.40
8b	65	EtOH	228-231	279	188	$C_{14}H_{13}N_7$	60.20 59.81	4.69 4.69	35.10 35.39
9a	70	EtOH	270-272	327	91	$C_{18}H_{13}N_7$	66.05 65.80	4.00 4.32	29.95 30.12
9b	71	EtOH	209-212	341	77	$C_{19}H_{15}N_7$	66.85 66.56	4.43 4.81	28.72 28.91
10a	95	MeOH	202-204	313	91	$C_{14}H_{15}N_7O_2$	53.67 53.51	4.83 5.10	31.29 31.26
10e	90	MeOH	205-207	347	125	$C_{14}H_{14}N_7O_2Cl$	48.35 48.27	4.06 3.71	28.19 28.53
10f	84	MeOH	208-209	331	109	$C_{14}H_{14}N_7O_2F$	50.75 50.42	4.26 3.99	29.59 29.42
11a	71	MeOH	265-270 dec	267	91	$C_{12}H_9N_7O$	53.93 54.15	3.39 3.53	36.69 36.92
11e	82	MeOH	258-269 dec	301	125	$C_{12}H_8N_7OCl$	47.77 47.46	2.67 2.49	32.50 32.48
11f	90	MeOH	256-266 dec	285	109	$C_{12}H_8N_7OF$	50.53 50.87	2.83 2.56	34.37 34.72

derivative **6a** in a low yield as a result of the concurrent formation of the hydroxy derivative **2a**, which could only be separated with difficulty.

We therefore followed an alternative synthetic route described in the literature [10] for the introduction of nucleophilic substituents in the 7 position of the triazolopyrimidine ring: the chloro derivatives **3a-d** reacted with thiourea in methanol to give the corresponding thiolderivatives **4a-d** in high yields, which, in turn, were easily converted to the methylthio derivatives **5a-d** with methyl iodide in an aqueous alkaline solution. By reaction with 99% hydrazine hydrate, these last compounds provided the expected hydrazino derivatives **6a-d** in ≈ 80% yields. The reactions of the benzylic series (compounds **1a-6a**) have been already

Scheme 2



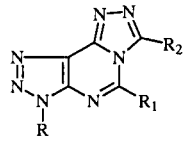
described in literature [10] but they were repeated for biological purposes. The intermediates **1b** [11], **1c**, **2c** [14] and **3c** [15] have also been previously described. Analogously to the cyclizations carried out on the triazolopyridazine derivatives [8], the hydrazino derivative **6a** was heated with formic acid to obtain the third 1,2,4-triazole heterocyclic ring, but the reaction proved to be unsatisfactory. The tricyclic compounds **7a-d** were subsequently obtained in good yield in accordance with the preparation of **7a** [2], by heating the hydrazino derivatives **6a-d** with triethyl orthoformate under reflux. By heating **6a,b** with triethyl orthoacetate in the same manner, the expected 3-methyl derivatives **8a** [2] and **8b** were obtained, while the reaction with triethyl orthobenzoate provided the 3-phenyl-substituted tricyclic compounds **9a** and **9b**. The appropriate 3-substituted-7-chlorotriazolopyrimidines **3a** (benzyl [10]), **3e** (2-chlorobenzyl [9]) and **3f** (2-fluorobenzyl [16]) (Scheme 2) reacted with ethyl carbazate in a benzene solution in the presence of triethylamine to give in high yields the corresponding triazolopyrimidine compounds **10a, e, f**, bearing the ethoxycarbonylhydrazino substituent in the 7 position. By heating **10a, e, f** at a high temperature (Dowtherm), an elimination of ethanol took place, thus forming the 1,2,4-triazole ring, and the expected 3-substituted-7-hydroxy-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo-[3,4-*c*]pyrimidines **11a, e, f** were obtained in good yields.

The structures of all the new compounds were assigned on the basis of the well-known reaction mechanism (1,3-dipolar cycloaddition of azides to activated methylenic compounds, formation of the pyrimidine ring, chlorination and nucleophilic displacement of the halogen by thiourea or hydrazine, formation of the fused 1,2,4-triazole ring) and were confirmed by analytical and spectroscopic data. Table 2 reports the ^{1}H-nmr spectral data of the tricyclic compounds **7, 8, 9** and **11**.

The tricyclic compounds **7, 8** and **9** were tested in radioligand binding assays for their affinity at A_1 and A_{2A} adenosine receptors in bovine brain cortical membranes and in bovine brain striatal membranes, respectively. The experiment, details of which have been reported in a previous paper [9], used [^{3}H]R-(-)-N^6-cyclohexyl-adenosine as the A_1 radioligand and [^{3}H]-2-{[[*p*-(2-carboxyethyl)-phenyl]ethyl]amino}-5'-(*N*-ethylcarbamoyl)adenosine (CGS-21680) as the A_{2A} radioligand. None of the compounds were found to possess any binding affinity.

Table II

^{1}H-NMR Data (δ) in Dimethyl-d$_6$ Sulfoxide of the Tricyclic Compounds



	R	R_1 and R_2
7a	7.32 (brs, 5H, C_6H_5), 5.95 (s, 2H, CH_2)	9.46 (s, lH, CH), 9.45 (s, lH, CH)
7b	7.20 (brs, 5H, C_6H_5), 5.0l (t, 2H, CH_2), 3, 38 (t, 2H, CH_2)	9.5l (s, lH, CH), 9.46 (s, lH, CH)
7c	2.25 (s, 3H, CH_3), 7.10 and 7.25 (AA'BB', 4H, C_6H_4), 5.86 (s, 2H, CH_2)	9.45 (s, 1H, CH), 9.43 (s, 1H, CH)
7d	2.44 (s, 3H, CH_3), 7.48 and 7.95 (AA'BB', 4H, C_6H_4)	9.86 (s, 1H, CH), 8.78 (s, 1H, CH)
8a	7.38 (brs, 5H, C_6H_5), 5.94 (s, 2H, CH_2)	9.66 (s, 1H, CH), 2.58 (s, 3H, CH_3)
8b	7.15 (brs, 5H, C_6H_5), 4.95 (t, 2H, CH_2), 3.33 (t, 2H, CH_2)	9.25 (s, 1H, CH), 2.80 (s, 3H, CH_3)
9a	7.35 (brs, 5H, C_6H_5), 5.97 (s, 2H, CH_2)	9.81 (s, 1H, CH), 8.21 (m, 2H, Ar), 7.56 (m, 3H, Ar)
9b	7.18 (brs, 5H, C_6H_5, 5.09 (t, 2H, CH_2), 3.36 (t, 2H, CH_2)	9.78 (s, 1H, CH), 8.24 (m, 2H, Ar), 7.56 (m, 3H, Ar)
11a	7.32 (brs, 5H, C_6H_5), 5.82 (s, 2H, CH_2)	8.75 (s, 1H, CH), 11. 10 (brs, 1H, exchangeable)
11e	7.57-7.08 (m, 4H, C_6H_4), 5.89 (s, 2H, CH_2)	8.75 (s, 1H, CH), 11.12 (brs, 1H, exchangeable)
11f	7.58-6.96 (m, 4H, C_6H_4), 5.86 (s, 2H, CH_2)	8.76 (s, 1H, CH), 11.16 (brs, 1H, exchangeable)

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. The ir spectra in nujol mulls were recorded on a Perkin-Elmer Mod. 1310 spectrometer. The ^{1}H nmr spectra were recorded with a Varian CFT-20 spectrometer in dimethyl-d$_6$ sulfoxide in δ units, using tetramethylsilane as the internal standard. Mass spectra were performed with a Hewlett Packard MS/System 5988. The tlc data were obtained with Riedel de Haen, 37360 DC-Karten F_{254}, 0.2 mm, eluting with a 1:2 AcOEt/60-80° petroleum ether mixture. Elemental analyses (C,H,N) were within ± 0.4% of theoretical values and were performed on a Carlo Erba Elemental Analyzer Mod. 1106 apparatus.

1-(4-Methylbenzyl)-4-carboxamido-5-amino-1*H*-1,2,3-triazole (**1c**).

To a stirred solution of sodium ethoxide, prepared with 0.780 g (34.0 g atoms) of sodium in 37 ml of absolute ethanol, 3.14 g (34.0 mmoles) of cyanacetamide was added. After 15 minutes, a solution of 4.80 g (32.6mmoles) of 4-methylbenzyl azide [14] in 15 ml of absolute ethanol was added to the suspension obtained. The reaction mixture was heated under reflux for 2 hours and after cooling, the solid precipitate was collected by filtration, washed with ethanol and dried (Table I).

3-Substituted-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyrimidines **2b** and **2c**.

A solution of 22.0 mmoles of the appropriate triazole derivative **1b** [11] or **1c** in 25 ml of formamide was refluxed for 2 hours. After cooling the reaction mixture was diluted with water, stirred for 3 hours and the solid precipitate was collected by filtration (Table I).

3-Substituted-7-chloro-1,2,3-triazolo[4,5-*d*]pyrimidines **3b** and **3c**.

To a suspension of 8.5 mmoles of the appropriate triazolopyrimidine **2b** or **2c** in 40 ml of boiling anhydrous chloroform, 1.5 ml of dimethylformamide and 7 ml of thionyl chloride were added. The reaction mixture was refluxed for 2 hours, the solvent was evaporated *in vacuo* (temperature ≤ 35°), and the residue, after cooling at 0°, was triturated with crushed ice. The solid formed was collected by filtration, dried and extracted repeatedly with boiling 60-80° petroleum ether. The combined extracts were evaporated *in vacuo* to give the title compounds as white solids (Table I).

3-Substituted-7-mercapto-1,2,3-triazolo[4,5-*d*]pyrimidines **4b, 4c** and **4d**.

A mixture of 6.0 mmoles of a suitable chloro derivative **3b**, **3c** or **3d** and 1.50 g (20.0 mmoles) of thiourea in 60 ml of anhydrous methanol was heated under reflux for 20 minutes. The reaction mixture was evaporated *in vacuo*, the residue was treated with 2% sodium hydroxide and the insoluble material was filtered. The filtrate was acidified (*p*H 4) with acetic acid to precipitate the title compounds which were collected, washed and dried (Table I).

3-Substituted-7-methylthio-1,2,3-triazolo[4,5-*d*]pyrimidines **5b, 5c** and **5d**.

To a stirred solution or suspension of 2.20 mmoles of the appropriate thio derivative **4b, 4c** or **4d** in 4-6 ml of 5% sodium hydroxide, 0.5-0.6 ml (8.0-9.6 mmoles) of methyl iodide was added and stirring was continued at room temperature for 1 hour. The solid precipitate was collected by filtration, washed with water and dried (Table I).

3-Substituted-7-hydrazino-1,2,3-triazolo[4,5-*d*]pyrimidines **6b, 6c** and **6d**.

A suspension of 2.50 mmoles of the appropriate methylthio derivative **5b, 5c** and **5d**, in 20 ml of anhydrous methanol was heated until it boiled, and then 2.5 ml (≈50 mmoles) of 99% hydrazine hydrate was added. The reaction mixture was stirred at room temperature for 1 hour and the crystalline solid formed, consisting of the title compounds, was collected, washed with methanol and dried (Table I).

3-Substituted-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidines **7b, 7c** and **7d**.

A solution of 0.80 mmole of **6b, 6c** or **6d** in 4 ml of triethyl orthoformate was heated under reflux for 8 hours. After cooling, the title compounds precipitated and were collected and washed with ethanol (Table I).

3-Phenethyl-7-methyl-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]-pyrimidine (**8b**).

A solution of 0.200 g (0.78 mmole) of **6b** in 3.5 ml of triethyl orthoacetate was heated at 140° for 8 hours. After cooling, **8b** precipitated as a crystalline solid which was collected by filtration and washed with methanol (Table I).

3-Substituted-7-phenyl-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]-pyrimidines **9a** and **9b**.

A solution of 1.0 mmole of the appropriate hydrazino derivative **6a** or **6b** in 2.5 ml of triethyl orthobenzoate was heated at 160° for 8 hours. After cooling, the title compounds crystallized from the reaction mixture and were collected by filtration and recrystallized (Table I).

3-Substituted-7-ethoxycarbonylhydrazino-1,2,3-triazolo[4,5-*d*]-pyrimidines **10a, 10e** and **10f**.

To a solution of 6.0 mmoles of the appropriate 3-substituted-7-chlorotriazolopyrimidine **3a, 3e** or **3f** in 65 ml of anhydrous benzene, 0.80 ml (6.0 mmoles) of triethylamine and 1.25 g (12.0 mmoles) of ethyl carbazate were added and the mixture was heated under reflux for 2 hours. The solvent was evaporated *in vacuo*, the residue was triturated with 50-60 ml of 10% hydrochloric acid and the insoluble material, consisting of the title compounds, was collected by filtration and washed with water (Table I).

3-Substituted-7-hydroxy-1,2,3-triazolo[4,5-*e*]1,2,4-triazolo[3,4-*c*]-pyrimidines **11a, 11e** and **11f**.

A solution of 1.50 mmoles of the appropriate derivative **10a, 10e or 10f** in 15 ml of Dowtherm was heated under reflux for 3 hours. After cooling the title compounds precipitated, the suspension was diluted with petroleum ether and the solid precipitated was collected by filtration and washed with petroleum ether (Table I).

REFERENCES AND NOTES

* Author for correspondence and reprint requests.

[1] A. Konnecke, R. Dorre, and E. Lippmann, *Tetrahedron Letters*, 2071 (1978).

[2] W. Ried and J. Laoutidis, *Chem.-Ztg.*, **114**, 246 (1990).

[3] P. G. Baraldi, L. Zappaterra, and E. Ongini, (Shering-Plough Spa) PCT Int. Appl. WO 95 01356; *Chem. Abstr.*, **122**, 239712 (1995).

[4] P .G. Baraldi, B. Cacciari, G. Spalluto, M. J. Pineda De Las Infants, C. Zocchi, S. Ferrara, and S. Dionisotti, *Farmaco*, **51**, 297 (1996).

[5] P. G. Baraldi, B. Cacciari, M. Viziano, S. Dionisotti, and E. Ongini, (Shering-Plough Spa) PCT Int. Appl. WO 97 05138; *Chem. Abstr.*, **126**, 212155 (1998).

[6] J. E. Francis, D. A. Bennett, J. L. Hyun, S. L. Rovinski, C. A. Amrick, P. S. Loo, D. Murphy, R. F. Neale, and D. E. Wilson, *J. Med. Chem.*, **34**, 2899 (1991).

[7] M. G. Collis and S. M. O. Hourani, *Trends Pharmacol. Sci.*, **14**, 360 (1993).

[8] G. Biagi, I. Giorgi, O. Livi, C. Manera, and V. Scartoni, *J. Heterocyclic Chem.*, **34**, 65 (1997).

[9] L. Betti, G. Biagi, G. Giannaccini, I. Giorgi, O. Livi, A. Lucacchini, C. Manera, and V. Scartoni, *J. Med Chem.*, **41**, 668 (1998).

[10] A. Albert, *J. Chem. Soc. C*, 152 (1969).

[11] G. Biagi, I. Giorgi, O. Livi, V. Scartoni, S. Velo, A. Lucacchini, G. Senatore, and P. L. Barili, *J. Heterocyclic Chem.*, **32**, 169 (1995).

[12] G. Biagi, I. Giorgi, O. Livi, V. Scartoni, S. Velo, C. Martini, G. Senatore, and P. L. Barili, *Farmaco.*, **50**, 99 (1995).

[13] Beilstein Handbuch der Organischen Chemie, **5**, Springer Ed., Berlin, **5**, III 773.

[14] A. Dornow and J. Helberg, *Chem. Ber.*, **93**, 2001 (1960).

[15] A. Da Settimo, O. Livi, P. L. Ferrarini, and G. Biagi, *Farmaco*, **35**, 308 (1980).

[16] R. Kreher and U. Bergman, *Tetrahedron Letters*, **47**, 4259 (1976).