Pyridazines. LIX [1]. Synthesis of *c*-Annelated Pyridazines from 3-Amino-4-pyridazinecarbonitrile

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The utility of the aminonitrile **1** as an educt for the preparation of several new examples of heterocycle-fused pyridazines (the [1,2,4]triazolo[1′,5′:1,6]pyrimido[4,5-*c*]pyridazine **7**, the pyrimido[4,5-*c*]pyridazines **8**, **10a,b**, and the pyrido[2,3-*c*]pyridazine **11**) is demonstrated.

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In continuation of our efforts directed towards the synthesis of bi- and tricyclic systems containing a pyridazine subunit [3-18], we here want to report on the annelation of pyridine and pyrimidine rings to a preformed 1,2-diazine system employing 3-amino-4-pyridazinecarbonitrile (**1**) as a conveniently accessible [10] precursor. Whereas 5-phenyl-3-amino-4-pyridazinecarbonitrile (**2**) has been shown by Stanovnik *et al.* [19] to be a versatile building block for the construction of a variety of polycyclic systems, the synthetic utility of compound **1**, which became available recently [10], so far remained unexplored.

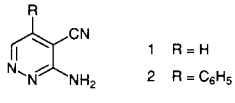


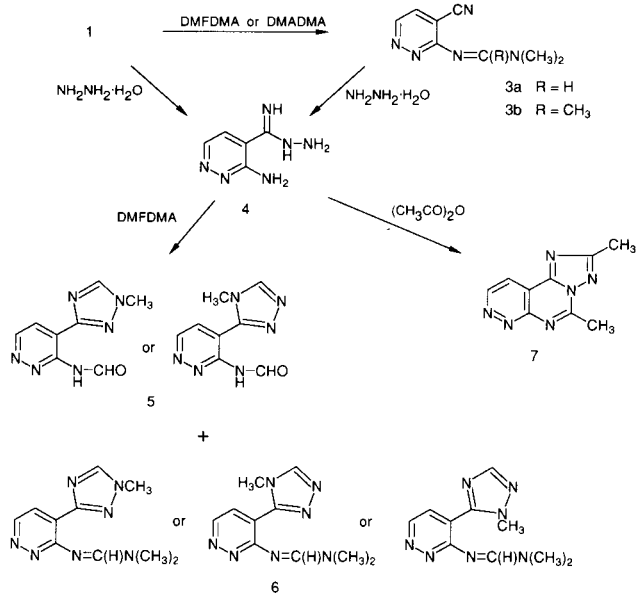
Figure 1

Treatment of the aminonitrile **1** with amide acetals like dimethylformamide dimethyl acetal (DMFDMA) or dimethylacetamide dimethyl acetal (DMADMA) smoothly led to the amidines **3a,b**. Reaction of the latter compounds with hydrazine hydrate - in analogy to ref [19]- resulted in formation of compound **4** by conversion of the cyano group into an amidrazone function and hydrolytic/-hydrazinolytic regeneration of the primary amino group. Other than observed with **2** [19], the nitrile function in **1** can be directly transformed into an amidrazone moiety (compound **4**) even without previous protection of the NH_2 group. This one-step route permits preparation of **4** from **1** in 85% yield.

Attempts to effect ring annelation by reacting compound **4** with excess DMFDMA (90°, 48 hours) failed. Instead, column chromatography of the reaction mixture afforded a compound $C_8H_8N_6O$ **5** (yield, 20%) along with a more polar product $C_{10}H_{13}N_7$ **6** (yield, 43%). A fragment ion m/e = 122 in the mass spectrum of **5** indicates the presence of an *N*-methyltriazolyl group (the methylating properties of DMFDMA are well known [20]) and thus excludes the participation of the original amidrazone function in any other ring closure reaction. The HN-CHO substructure in **5** clearly follows from ^{1}H-nmr and ir data (see Experimental). Homonuclear NOE experiments (irradiation either at 4.03 or 8.87 ppm) unambiguously indicate a vicinal position of the triazole-H and the *N*-methyl group, thus suggesting the two alternative structures **5** for this compound. The three isomeric structures shown in formulae **6** appear to be the most probable ones for the main product, according to the elemental composition determined and the ^{1}H-nmr data [21]. Again, formation of a triazole ring, followed by its *N*-methylation, may be assumed; conversion of the remaining amino group into an *N,N*-dimethylaminomethyleneamino moiety seems to be a reasonable consequence [22].

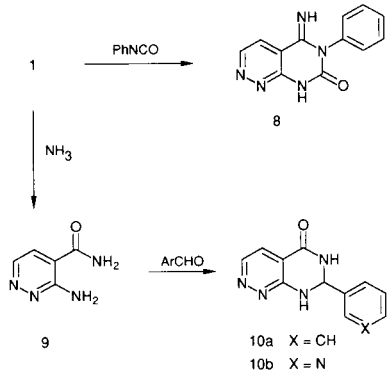
On the other hand, reaction of **4** with acetic anhydride indeed gave a tricyclic compound **7**. The microanalytical and spectroscopic data of this product call for either a [1,2,4]triazolo[1′,5′:1,6]pyrimido- or a [1,2,4]triazolo[3′,4′:-1,6]pyrimido[4,5-*c*]pyridazine structure. The former one, however, appears to be the more reasonable assumption for thermodynamic reasons [23].

Scheme 1



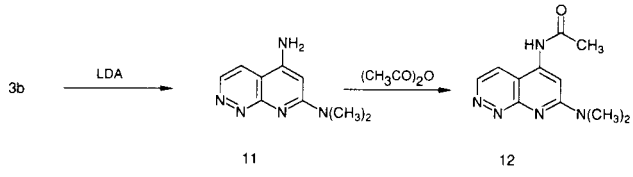
Starting from the amino nitrile **1**, annelation of a pyrimidine ring could be achieved by treatment with phenyl isocyanate. Since compound **8** thus obtained in satisfactory yield turned out to be partially hydrolysed on attempted purification, the elemental composition was determined by high-resolution mass spectrometry. Moreover, the aminonitrile **1** also permits a convenient access to 7,8-dihydro-7-arylpyrimido[4,5-*c*]pyridazin-5(6*H*)-ones **10a,b**, which are of interest in view of the reported pharmacological properties (diuretic activity) of closely related pyridopyrimidones [24]. In this case, **1** was converted into the amide **9** in 65% yield by refluxing in aqueous ammonia [25]; subsequent condensation with benzaldehyde or 3-pyridinecarbaldehyde then gave the bicyclic compounds **10a,b**.

Scheme 2



Finally, also pyridine ring annelation could be accomplished as displayed in Scheme 3. Here, an approach involving C-C bond formation by employing the acetamidine derivative **3b**, was chosen. Other than previously observed in the synthesis of pyrido[2,3-*d*]pyridazines [7], intramolecular cyclisation of **3b** was found to require deprotonation of the amidine methyl group by a strong base. Thus, treatment of **3b** with lithium diisopropylamide (LDA) at -70° (in analogy to ref [27]) afforded the pyrido-[2,3-*c*]pyridazine derivative **11**. As the base **11** proved to be of low stability, it was converted into the corresponding *N*-acetyl compound **12**, which then could be conveniently characterized.

Scheme 3



EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra were recorded for potassium bromide pellets on a Jasco IRA-1 spectrophotometer. The ^{1}H-nmr spectra were recorded on a Bruker AC 80 (80 MHz) spectrometer (TMS as the internal reference). Mass spectra and high-resolution mass spectra were obtained on Finnigan MAT 311A and Finnigan MAT 8230 instruments (70 eV). For tlc, Merck aluminium sheets pre-coated with Kieselgel 60 F_{254} were used; column chromatography was carried out on Merck Kieselgel 60 (70-230 mesh), medium-pressure liquid chromatography (mplc) was performed on Merck LiChroprep Si 60 (230-400 mesh), detection at 280 nm. Light petroleum refers to the fraction of bp 50-70°.

3-(*N*,*N*-Dimethylaminomethyleneamino)-4-pyridazinecarbonitrile (**3a**).

A mixture of 120 mg (1 mmole) of 3-amino-4-pyridazinecarbonitrile (**1**) [10] and 1.5 ml of DMFDMA was heated to 120° for 2 hours. After cooling, the precipitate was filtered off, washed with cold cyclohexane and recrystallised from ethyl acetate-light petroleum to afford 154 mg (88%) of pale yellow needles, mp 112-113°; ^{1}H-nmr (deuteriochloroform): δ 8.87 (d, J = 5 Hz, H-6, 1 H), 8.80 (s, N=CH-N, 1 H), 7.48 (d, J = 5 Hz, H-5, 1 H), 3.22 (s, CH_3, 6 H); ir: cm^{-1} 2240 (CN).

Anal. Calcd. for $C_8H_9N_5$: C, 54.85; H, 5.18; N, 39.97. Found: C, 54.91; H, 5.23; N, 39.98.

3-[1-(*N*,*N*-Dimethylamino)ethylideneamino]-4-pyridazinecarbonitrile (**3b**).

A mixture of 120 mg (1 mmole) of **1** [10] and 1.5 ml of DMA-DMA was heated to 120° for 2 hours. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (dichloromethane-methanol, 14:1), followed by recrystallisation from ethyl acetate-light petroleum to give 113 mg (60%) of pale yellow crystals, mp 104-106°; ^{1}H-nmr (deuteriochloroform): δ 8.82 (d, J = 5 Hz, H-6, 1 H), 7.48 (d, J = 5 Hz, H-5, 1 H), 3.20 (s, NCH_3, 6 H), 2.27 (s, CH_3, 3 H); ir: cm^{-1} 2240 (CN).

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.19; H, 5.95; N, 36.76.

3-Amino-4-pyridazinecarboxamidrazone (**4**).

A solution of 120 mg (1 mmole) of **1** [10] in 3 ml of hydrazine hydrate (99-100%) was stirred at room temperature for 5 days. The precipitate was filtered off and recrystallised from ethanol to afford 129 mg (85%) of almost colorless crystals, mp 199-203°; in an analogous manner, compound **4** can be prepared from **3a** (yield, 66%) or from **3b** (yield, 40%); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 8.45 (d, J = 5 Hz, H-6, 1 H), 7.55 (br, NH, 2 H), 7.46 (d, J = 5 Hz, H-5, 1 H), 5.79 (br, NH, 2 H), 5.51 (br, NH, 2 H).

Anal. Calcd. for $C_5H_8N_6$: C, 39.47; H, 5.30; N, 55.23. Found: C, 39.47; H, 5.28; N, 54.95.

Reaction of Compound **4** with Dimethylformamide Dimethyl Acetal.

A mixture of 152 mg (1 mmole) of the amidrazone **4** and 5 ml of DMFDMA was heated to 90° for 2 days. The volatile components were removed *in vacuo* and the residue was subjected to column chromatography (dichloromethane-methanol, 9:1) and subsequently to mplc (dichloromethane-methanol, 94:6).

Recrystallisation of the first fraction from ethanol afforded 41 mg (20%) of compound **5**, *i.e.* *N*-[4-(1-methyl-1*H*-1,2,4-triazol-3-yl)-3-pyridazinyl]formamide or *N*-[4-(4-methyl-4*H*-1,2,4-triazol-3-yl)-3-pyridazinyl]formamide, as tiny, colorless needles, mp

236-239°; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 10.90 (br, NH, exchangeable with deuterium oxide, 1 H), 9.68 (d, J = 10 Hz, s after addition of deuterium oxide, formyl-H, 1 H), 9.13 (d, J = 5.5 Hz, pyridazine-H, 1 H), 8.87 (s, N=CH-N, shows NOE on irradiation at 4.03 ppm, 1 H), 8.20 (d, J = 5.5 Hz, pyridazine-H, 1 H), 4.03 (s, CH_3, shows NOE on irradiation at 8.87 ppm, 3 H); ir: cm^{-1} 1680 (CO), 1560 (NH); ms: m/e 204 (M^+, 24), 176 (100), 122 (22), 108 (63); hrms: m/e Calcd. for $C_8H_8N_6O$: 204.0760; Found: 204.0770.

Anal. Calcd. for $C_8H_8N_6O$: C, 47.06; H, 3.95; N, 41.16. Found: C, 46.86; H, 3.97; N, 41.26.

Recrystallisation of the second fraction from ethyl acetate afforded 99 mg (43%) of compound **6**, *i.e.* 3-(*N*,*N*-dimethylaminomethyleneamino)-4-(1-methyl-1*H*-1,2,4-triazol-3-yl)pyridazine or 3-(*N*,*N*-dimethylaminomethyleneamino)-4-(4-methyl-4*H*-1,2,4-triazol-3-yl)pyridazine or 3-(*N*,*N*-dimethylaminomethyleneamino)-4-(1-methyl-1*H*-1,2,4-triazol-5-yl)pyridazine, as tiny, pale yellow needles, mp 163-164°; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 8.93 (d, J = 5 Hz, pyridazine-H, 1 H), 8.70 (s, N=CH-N, 1 H), 8.01 (s, N=CH-N, 1 H), 7.57 (d, J = 5 Hz, pyridazine-H, 1 H), 3.77 (s, CH_3, 3 H), 3.14 (s, CH_3, 3 H), 2.91 (s, CH_3, 3 H); ms: m/e 231 (M^+, 65), 188 (34), 44 (38), 42 (100); hrms: m/e Calcd. for $C_{10}H_{13}N_7$: 231.1232; Found: 231.1228.

Anal. Calcd. for $C_{10}H_{13}N_7$: C, 51.94; H, 5.67; N, 42.40. Found: C, 51.87; H, 5.60; N, 42.67.

2,5-Dimethyl[1,2,4]triazolo[1',5':1,6]pyrimido[4,5-*c*]pyridazine (**7**).

A mixture of 152 mg (1 mmole) of the amidrazone **4** and 4 ml of acetic anhydride was heated to 80° for 20 hours. The volatile components were removed *in vacuo* and the residue was subjected to column chromatography (dichloromethane-methanol, 9:1) and subsequently to mplc (dichloromethane-methanol, 94:6). Recrystallisation from ethyl acetate gave 91 mg (45%) of hygroscopic, pale yellow crystals, mp 199-203°; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 9.61 (d, J = 5.5 Hz, H-9, 1 H), 8.57 (d, J = 5.5 Hz, H-10, 1 H), 3.00 (s, CH_3, 3 H), 2.63 (s, CH_3, 3 H).

Anal. Calcd. for $C_9H_8N_6 \cdot 1/8H_2O$: C, 53.39; H, 4.11; N, 41.51. Found: C, 53.56; H, 4.04; N, 41.51.

5,6,7,8-Tetrahydro-5-imino-7-oxo-6-phenylpyrimido[4,5-*c*]pyridazine (**8**).

A solution of 120 mg (1 mmole) of **1** [10] and 238 mg (2 mmoles) of phenyl isocyanate in 15 ml of dimethyl formamide was refluxed for 24 hours. After cooling, the mixture was poured onto ice. The precipitate was filtered off, washed with aqueous sodium hydrogencarbonate and water, and dried. Recrystallisation from ethyl acetate afforded 180 mg (75%) of an almost colorless powder, mp 240-250°; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 12.4-9.6 (br, NH, 2 H), 9.21 (d, J = 5 Hz, H-3, 1 H), 8.42 (d, J = 5 Hz, H-4, 1 H), 7.70-7.10 (m, phenyl-H, 5 H); ir: cm^{-1} 1650 (CO); hrms: m/e Calcd. for $C_{12}H_9N_5O$: 239.0807; Found: 239.0812.

3-Amino-4-pyridazinecarboxamide (**9**) [26].

A solution of 120 mg (1 mmole) of **1** in 3.5 ml of 1% aqueous ammonia was refluxed for 24 hours. After cooling, the precipitate was filtered off, washed with cold ethanol, and recrystallised from ethanol-water to give 90 mg (65%) of pale yellow crystals, mp 244-245° (ref [26] mp 244-245°).

7,8-Dihydro-7-phenylpyrimido[4,5-*c*]pyridazin-5(6*H*)-one (**10a**).

A mixture of 138 mg (1 mmole) of the amide **9** and 1.4 ml of benzaldehyde was heated to 180° for 3 hours. After cooling, the solution was diluted with cyclohexane. The precipitate was filtered off, washed with cyclohexane, and recrystallised from ethanol to afford 149 mg (65%) of pale yellow crystals, mp 230-233°; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 9.01 (br, NH, 1 H), 8.71 (d, J = 4.5 Hz, H-3, 1 H), 8.51 (br, NH, 1 H), 7.62 (d, J = 4.5 Hz, H-4, 1 H), 7.45-7.35 (m, phenyl-H, 5 H), 5.96 (d, J = 2.4 Hz, H-7, 1 H); ir: cm^{-1} 1660 (CO).

Anal. Calcd. for $C_{12}H_{10}N_4O \cdot 1/8H_2O$: C, 63.08; H, 4.52; N, 24.52. Found: C, 63.23; H, 4.55; N, 24.49.

7,8-Dihydro-7-(3-pyridyl)pyrimido[4,5-*c*]pyridazin-5(6*H*)-one (**10b**).

A mixture of 138 mg (1 mmole) of **9** and 1.4 ml of 3-pyridinecarbaldehyde was heated to 140° for 3 hours. The excess aldehyde was removed *in vacuo* and the residue was triturated with cyclohexane, filtered off, and recrystallised from ethanol to yield 130 mg (55%) of pale yellow crystals, mp 221-224°; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 9.02 (br, NH, 1 H), 8.75 (d, J = 4.5 Hz, H-3, 1 H), 8.63-8.53 (m, NH, pyridine H-2, H-6, 3 H), 7.92-7.82 (m, pyridine H-4, 1 H), 7.65 (d, J = 4.5 Hz, H-4, 1 H), 7.51-7.36 (m, pyridine H-5, 1 H), 6.09 (d, unresolved, H-7, 1 H); ir: cm^{-1} 1670 (CO).

Anal. Calcd. for $C_{11}H_9N_5O \cdot 1/2H_2O$: C, 55.93; H, 4.27; N, 29.65. Found: C, 55.82; H, 4.30; N, 29.48.

5-Amino-7-dimethylaminopyrido[2,3-*c*]pyridazine (**11**).

To a solution of 0.168 ml (1.2 mmoles) of diisopropylamine in 5 ml of dry tetrahydrofuran, kept at -70° under an atmosphere of argon, were added dropwise 0.75 ml (1.2 mmoles) of a 1.6 *M* solution of *n*-butyllithium in hexane. After stirring for 10 minutes at -70°, the solution was allowed to warm to room temperature. Then, the mixture again was cooled to -70°, and a solution of 189 mg (1 mmole) of compound **3b** in 10 ml of dry tetrahydrofuran was added slowly. The solution was stirred at -70° for 30 minutes, then stirring was continued at room temperature for 1 hour. After addition of 2 ml of saturated aqueous ammonium chloride, the mixture was evaporated *in vacuo*. The residue was subjected to column chromatography (dichloromethane-methanol, 5:1) and subsequently to mplc (dichloromethane-methanol, 6:1) to afford 120 mg (64%) of a yellow solid, mp 255-270° dec, which slowly turned dark; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 8.92 (d, J = 5.5 Hz, H-3, 1 H), 8.11 (d, J = 5.5 Hz, H-4, 1 H), 6.88 (br, NH, 2 H), 6.26 (s, H-6, 1 H), 3.16 (s, CH_3, 6 H); ms: m/e 189 (M^+, 4), 174 (11), 45 (100); hrms: m/e Calcd. for $C_9H_{11}N_5$: 189.1014; Found: 189.1022.

5-Acetylamino-7-dimethylaminopyrido[2,3-*c*]pyridazine (**12**).

A mixture of 30 mg (0.16 mmole) of compound **11** and 5 ml of acetic anhydride was stirred at room temperature for 4 days. The volatile components were removed *in vacuo* and the residue was purified by column chromatography (dichloromethane-methanol, 6:1), followed by recrystallisation from ethanol to give 28 mg (76%) of tiny yellow needles, mp 275-298° dec; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 10.16 (br, NH, 1 H), 9.07 (d, J = 5.5 Hz, H-3, 1 H), 8.25 (d, J = 5.5 Hz, H-4, 1 H), 8.03 (s, H-6, 1 H), 3.23 (s, NCH_3, 6 H), 2.25 (s, CH_3, 3 H); ir: cm^{-1} 1700 (CO).

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 56.91; H, 5.49; N, 30.03.

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schuljubiläumsstiftung der Stadt Wien'' is gratefully acknowledged.

REFERENCES AND NOTES

[1] As part **58** of this series counts: G. Heinisch, W. Holzer and T. Huber, *Monatsh. Chem.*, in the press.

[2] Taken in part from the Diploma Thesis of R. Wanko, University of Vienna, Austria, 1989.

[3] G. Heinisch and I. Kirchner, *Monatsh. Chem.*, **110**, 365 (1979).

[4] N. Haider, G. Heinisch and I. Kirchner, *Arch. Pharm. (Weinheim)*, **315**, 778 (1982).

[5] N. Haider and G. Heinisch, *J. Chem. Soc., Perkin Trans. 1*, 169 (1986).

[6] N. Haider and G. Heinisch, *Arch. Pharm. (Weinheim)*, **319**, 850 (1986).

[7] N. Haider and G. Heinisch, *Synthesis*, 862 (1986).

[8] G. Heinisch and D. Laßnigg, *Arch. Pharm. (Weinheim)*, **320**, 1222 (1987).

[9] N. Haider and G. Heinisch, *J. Chem. Soc., Perkin Trans. 1*, 401 (1988).

[10] N. Haider, G. Heinisch and D. Laßnigg, *J. Heterocyclic Chem.*, **25**, 119 (1988).

[11] W. Dostal, G. Heinisch and G. Lötsch, *Monatsh. Chem.*, **119**, 751 (1988).

[12] P. Y. Boamah, N. Haider, G. Heinisch and J. Moshuber, *J. Heterocyclic Chem.*, **25**, 879 (1988).

[13] N. Haider and G. Heinisch, *Arch. Pharm. (Weinheim)*, **321**, 309 (1988).

[14] P. Y. Boamah, N. Haider and G. Heinisch, *J. Heterocyclic Chem.*, **26**, 933 (1989).

[15] N. Haider, G. Heinisch and I. Volf, *Heterocycles*, **29**, 1309 (1989).

[16] M. Grabenwöger, N. Haider and G. Heinisch, *Liebigs Ann. Chem.*, 481 (1989).

[17] P. Y. Boamah, N. Haider and G. Heinisch, *Arch. Pharm. (Weinheim)*, **323**, 207 (1990).

[18] K. Czech, N. Haider and G. Heinisch, *Monatsh. Chem.*, **122**, 413 (1991).

[19] B. Stanovnik, V. Stibilj and M. Tisler, *Synthesis*, 807 (1986).

[20] B. Stanovnik, M. Tisler, A. Hribar, G. B. Barlin and D. J. Brown, *Aust. J. Chem.*, **34**, 1729 (1981).

[21] Besides the pyridazine-H signals, the ^{1}H-nmr spectrum (deuteriodimethyl sulfoxide) shows two low-field singulets (8.70 and 8.01 ppm) and three separated N-CH_3 resonances. Since H-D exchange could not be observed, any structures containing an N-H group appear to be very unlikely. Other than with compound **5**, NOE experiments do not provide additional information.

[22] It should be mentioned that an unambiguous structure proof for compounds **5** and **6** at present cannot be provided as we so far did not succeed in the preparation of crystals suitable for X-ray analysis.

[23] C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Ananthan and V. S. Bhadti, *J. Heterocyclic Chem.*, **24**, 1125 (1987).

[24] H. A. Parish, R. D. Gilliom, W. P. Purcell, R. K. Browne, R. F. Spirk and H. D. White, *J. Med. Chem.*, **25**, 98 (1982).

[25] This procedure represents a much more convenient access to **9** than the route previously reported by Yanai *et al.* [26].

[26] M. Yanai, T. Kinoshita, H. Watanabe and S. Iwasaki, *Chem. Pharm. Bull.*, **19**, 1849 (1971).

[27] S. F. Campbell, J. D. Hardstone and M. J. Palmer, *Tetrahedron Letters*, 4813 (1984).