Polycondensed Nitrogen Heterocycles. Part 24. Pyrrolo[3,4-*c*]isoquinolinone by Thermal Rearrangement of a Pyrrolylbenzotriazinone

Girolamo Cirrincione*, Anna Maria Almerico, Gaetano Dattolo, Enrico Aiello, Patrizia Diana and Francesco Mingoia

Istituto Farmacochimico dell'Università
di Palermo, Via Archirafi 32,
90123 Palermo, Italy

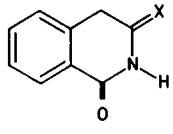
Received March 26, 1992

Rearrangement under acidic conditions of the pyrrolylbenzotriazinone **7** afforded the pyrrolylbenzamides **10** and **11**. By thermal rearrangement instead, the first fully aromatic derivative of the pyrrolo[3,4-*c*]isoquinoline ring system **9** was obtained.

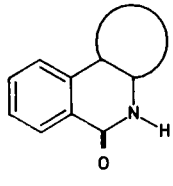
J. Heterocyclic Chem., **29**, 1309 (1992).

The occurrence of the isoquinoline nucleus in compounds of biological interest, either from natural or synthetic sources, is indicated by the large number of reports dealing with their pharmaceutical properties. In fact, for example, they have antimicrobial activity [1], cardiovascular effects [2], and diuretic properties [3]. Because of the pharmaceutical interest of this class of compounds, several studies on the ability of isoquinoline derivatives to inhibit enzymes such as human monoamino oxidase [4], protein kinase [5], and angiotensin converting enzyme [6] are also reported.

In particular isoquinolin-3-ones and isoquinolinones of type **1** (X = O, S) have shown antiallergic activity [7], are herbicides [8], plant growth regulators [9], and antitumor agents against HeLa and Ehlrich ascite carcinoma [10]. Moreover condensed isoquinoline derivatives show enhanced biological properties. Thus compounds of type **2**, annelated on the 3,4-positions of the isoquinoline nucleus, such as pancratistatine, crinasiadine and lycoricidine, isolated from roots and bulbs of *Amaryllidaceae*, possess antineoplastic activity [11]. Derivatives of type **2** condensed with heterocyclic moieties such as indole, indazole and pyrazole are active against fungi and bacteria [12] or show antiinflammatory or antihypertensive activities [13].



1

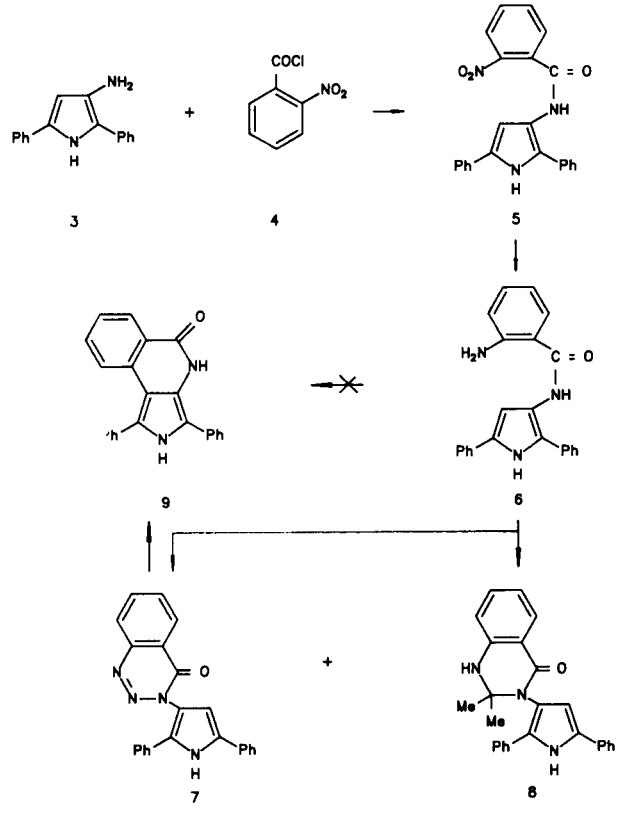


2

Therefore, in connection with our researches on biologically active polycondensed nitrogen heterocycles containing a pyrrole moiety, we became interested in the synthesis of pyrrolo[3,4-*c*]isoquinolinone derivatives. Actually this pyrroloisoquinoline ring system has been already synthesized, but the compounds of this series have been incidentally prepared as a result of cycloaddition or cyclocondensation reactions and all of them are polyhydrogenated [14-17].

Thus to obtain fully aromatic derivatives, the aminopyrrole **3** was condensed with 2-nitrobenzoyl chloride **4** to give in excellent yield the 2-nitrobenzamido derivatives **5**. Catalytic reduction of the nitro group of **5** led, in 95% yield, to the corresponding amino derivative **6**. The Pschorr reaction of compound **6** would give rise to the polycondensed pyrroloisoquinoline derivative **9** through a cyclization reaction leading to the formation of the C-4/C-4a bond of the isoquinoline nucleus. The competitive cy-

Scheme 1



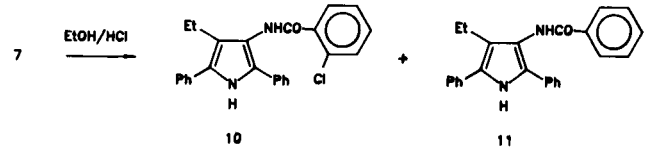
clization reaction with the amido nitrogen, leading to the pyrrolylbenzotriazinone **7**, could be avoided carrying out the diazotization reaction at high temperature (60-80°) in order to favour the dediazoniation reaction. Therefore the amine **6** was diazotized in acetone with sodium nitrite and 2*N* sulfuric acid at 60°. From the reaction mixture it was possible to isolate the triazinone derivative **7** (50% yield), together with compound **8** (20% yield).

Evidently the pyrroloisoquinoline **9** was not formed even under these experimental conditions because the intermediate diazonium salt is so reactive that the intramolecular coupling reaction takes place before it can be decomposed. The structure **7** was assigned on the basis of the spectroscopic data. The mass spectrum showed a molecular ion in agreement with retention of nitrogen and a fragmentation pattern, involving sequential loss of nitrogen and carbon monoxide, which is usual for benzotriazinone derivatives [18-19]. Furthermore in the ^{1}H nmr spectrum, the presence of a doublet at 6.90 δ (J = 1.5 Hz), that became a singlet upon exchange with deuterium oxide, attributable to the pyrrole β-proton allowed to discard the isomeric pyrrolobenzotriazocine structure which could be obtained by intramolecular coupling reaction with the β-position of the pyrrole nucleus.

The formation of derivative **8** was due to the condensation of the unreacted amino compound **6** with acetone followed by ring closure of the ketimino carbon with the amide nitrogen. The structure **8** was assigned essentially on the basis of the ^{13}C nmr spectrum in which the carbon atom bearing the two methyl groups is found at 72.46 ppm whereas the isomeric open-chain Schiff's base should have the corresponding signal at about 155-160 ppm.

Considering that it was impossible to avoid the formation of the pyrrolylbenzotriazinone derivative **7**, we thought to optimize the yield of this compound because it could be useful as key intermediate to obtain the pyrroloisoquinolinone **9** since it is well recognized that 3-substituted benzotriazinones behave as masked diazonium salts under opportune reaction conditions. In fact 3-arylbenzotriazin-4-ones show a remarkable thermal stability, but undergo ring scission between N-2 and N-3 to generate the diazonium species which rearrange with loss of nitrogen [20]. The same type of conversion can be achieved under milder conditions using acidic media [21]. Thus the diazotization reaction of the amino derivative **6**, carried out at room temperature in acetic acid, led to **7** in quantitative yield. The benzotriazinone **7** was heated in absolute ethanol saturated with hydrogen chloride. From the reaction mixture, it was possible to isolate the pyrrole derivatives **10** and **11** in 27% and 10% yields respectively.

Scheme 2



10 11

Probably the cyclization reaction to pyrroloisoquinoline did not occur since the ethylation of the pyrrole nucleus preceded the decomposition of the diazonium ion. Therefore typical reactions of diazonium salts leading either to the chloro compound **10** and to the corresponding dediazoniated derivative **11** were observed. The structure of these compounds was assigned on the basis of spectroscopic data. In fact besides the appearence of an additional band in the range 3356-3410 cm^{-1} due to the amide NH stretching vibrations in the ir spectra, the ^{1}H nmr spectra showed a lack of signals attributable to pyrrole β-proton and the presence of triplet-quartet signals (J = 6.0 Hz) centered at 1.11-1.18 δ and 2.32-2.49 δ respectively, typical of an ethyl group bound to an aromatic carbon. In the ^{13}C nmr spectra the corresponding signals were found at 15.12-15.41 ppm and 17.06-17.18 ppm respectively.

Because of the failure of the rearrangement in acidic medium, the thermal rearrangement was undertaken. Thus the benzotriazinone **7** was thermolyzed at 220° for 6 hours, but only unreacted starting material was recovered. Therefore the thermolysis was carried out at 250°. After 3 hours the benzotriazinone was completely decomposed and a tarry, gummy residue was obtained from which it was possible to isolate only one identifiable compound. The analytical and spectroscopic data are in agreement with the pyrrolo[3,4-*c*]isoquinolinone structure **9** assigned to the product of thermolysis (25% yield). In particular, the ir spectrum had two absorption bands at 3380 and 3200 cm^{-1} attributable to the NHs and a band at 1640 cm^{-1} due to the carbonyl stretching. The ^{1}H nmr spectrum showed two broad peaks at 8.27 and 10.69 δ attributable to the two iminic protons whereas in the ^{13}C nmr spectrum the presence of a peak at 161.59 ppm due to the carbonyl carbon atom is in agreement with the reported values for the C-2 of pyridin-2-one derivatives [22].

In conclusion, this procedure represents the first method to prepare fully aromatic pyrrolo[3,4-*c*]isoquinoline derivatives although in low yields. Probably better yields could be obtained by using alternative syntheses, as for example the decomposition of suitable arylnitrenium ions.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; ir spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer; ^{1}H and ^{13}C nmr spectra were measured at 100 and 25 MHz respectively in DMSO-d_6 solution, unless otherwise specified, using a JEOL FX-100 spectrometer (TMS as internal reference); mass spectra were obtained with a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV

and 10 Kv accelerating voltage. Column chromatography was performed with Merck silica gel 230-400 Mesh ASTM.

Preparation of 2,5-Diphenyl-3-(2-nitrobenzamido)pyrrole (**5**).

To an ice cooled and stirred solution of 3-amino-2,5-diphenylpyrrole (**3**) [23] (4.68 g, 20 mmoles) and triethylamine (20 mmoles) in anhydrous dichloromethane (100 ml), a solution of 2-nitrobenzoyl chloride (**4**) (3.7 g, 20 mmoles) in anhydrous dichloromethane (20 ml) was added dropwise. The reaction mixture was allowed to reach room temperature and after 4 hours the solvent was evaporated under reduced pressure. The residue was shaken for 30 minutes with water (200 ml), added with few drops of hydrochloric acid, filtered, and the solid was washed with a saturated aqueous solution of sodium hydrogen carbonate. The dried solid residue was recrystallized from benzene/ethanol 1:1 (yield 92%), mp 209°; ir: 3440, 3380 (NH), 1665 (CO) cm^{-1}; ^1H nmr (acetone-d_6): δ 7.04 (1H, d (J = 2.0 Hz), singlet upon exchange with deuterium oxide pyrrole H-4), 7.19-7.45 (6H, m, ArH), 7.67-7.87 (6H, m, ArH), 7.99-8.10 (2H, m, ArH), 9.25 (1H, bs, exchangeable NH), 10.46 (1H, bs, exchangeable NH); ms: m/z M^+ = 383.

Anal. Calcd. for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.01; H, 4.52; N, 10.89.

Preparation of 3-(2-Aminobenzamido)-2,5-Diphenylpyrrole (**6**).

The nitro derivative **5** (10 mmoles) dissolved in ethanol (100 ml) was reduced with 10% Pd on charcoal in a Parr apparatus at 45 psi for 12 hours at room temperature. The catalyst was filtered off and the concentrate solution was allowed to crystallize (yield 95%), mp 196-197°; ir: 3470, 3380 and 3280 (broad) (NH_2 and NH), 1660 (CO) cm^{-1}; ^1H nmr: δ 6.42 (2H, s, exchangeable NH_2), 6.54-6.67 (2H, m, ArH), 6.76 (1H, d (J = 2.0 Hz), singlet upon exchange with deuterium oxide, pyrrole H-4), 7.10-7.46 (7H, m, ArH), 7.66-7.81 (5H, m, ArH), 9.49 (1H, s, exchangeable CON*H*), 11.17 (1H, bs, exchangeable pyrrole NH); ms: m/z M^+ = 353.

Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.24; H, 5.50; N, 11.69.

Diazotization of 3-(2-Aminobenzamido)-2,5-diphenylpyrrole.

Method A. Diazotization in Sulfuric Acid.

The amine **6** (5 mmoles) was dissolved in the minimum volume of acetone and sulfuric acid (2*N*, 30 ml) was added. The reaction mixture was heated at 60° and sodium nitrite (5 mmoles) in water (3 ml) was added. The mixture was kept at the same temperature for 1 hour and then the acetone was evaporated. After cooling, aqueous sodium hydroxide (1*N*) was added until the *p*H was adjusted to *ca* 7. The solid precipitate was filtered off and dried. The crude product was chromatographed using dichloromethane as eluant. The first product eluted was the 3-(2,5-diphenylpyrrole-3-yl)benzotriazin-4-one (**7**) (yield 50%), mp 209°; ir: 3335 (NH), 1684 (CO) cm^{-1}; ^1H nmr: δ 6.90 (1H, d (J = 1.5 Hz), singlet upon exchange with deuterium oxide, pyrrole H-4), 7.21-7.59 (10H, m, ArH), 7.83-8.43 (4H, m, ArH), 11.79 (1H, bs, exchangeable NH); ms: m/z (relative intensity) 364 (M^+, 20), 336 (80), 308 (25), 256 (50), 149 (100), 105 (70), 77 (55).

Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 75.77; H, 4.41; N, 15.29.

Further elution gave 2,2-dimethyl-3-(2,5-diphenylpyrrole-3-yl)-2,3-dihydro-1*H*-quinazolin-4-one (**8**) (yield 20%), mp 270°; ir: 3380 and 3260 (NH), 1680 (CO) cm^{-1}; ^1H nmr: δ 1.11 (3H, s, CH_3), 1.54 (3H, s, CH_3), 6.60 (1H, d (J = 2.3 Hz), singlet upon exchange with deuterium oxide, pyrrole H-4), 6.71-6.77 (2H, m, ArH), 6.86 (1H, s, exchangeable NH), 7.16-7.42 (7H, m, ArH), 7.65-7.84 (5H, m, ArH), 11.36 (1H, bs, exchangeable NH); ^{13}C nmr: δ 26.52 (q), 27.09 (q), 72.46 (s), 107.94 (d), 114.51 (s), 114.99 (d), 116.90 (d), 120.22 (s), 123.85 (d), 125.85 (s), 125.95 (d), 126.21 (s), 127.85 (s), 128.15 (d), 128.46 (d), 128.68 (d), 130.48 (d), 131.82 (d), 132.17 (s), 133.15 (s), 146.66 (d), 163.27 (s); ms: m/z M^+ = 393.

Anal. Calcd. for $C_{26}H_{23}N_3O$: C, 79.36; H, 5.90; N, 10.68. Found: C, 79.42; H, 5.79; N, 10.70.

Method B. Diazotization in Acetic Acid.

The amine **6** (5 mmoles) was dissolved in glacial acetic acid (25 ml) and sodium nitrite (5 mmoles) dissolved in water (3 ml) was added dropwise under stirring at room temperature. The reaction mixture was stirred for 1 hour and then poured onto crushed ice. The solid precipitate was collected and recrystallized to give the benzotriazinone derivative **7** in quantitative yield.

Decomposition of the Pyrrolylbenzotriazinone **7** in Ethanolic Hydrogen Chloride.

Benzotriazinone (**7**) (2 mmoles) was refluxed in absolute ethanol saturated with gaseous hydrogen chloride (30 ml) until no starting material was detected by tlc (2 hours). The solvent was evaporated under reduced pressure and the solid residue was triturated with water and the *p*H adjusted to 7 with aqueous sodium bicarbonate. The solid was collected, air dried and chromatographed using dichloromethane as eluant. The first product eluted was 3-(2-chlorobenzamido)-2,5-diphenyl-4-ethylpyrrole (**10**) (yield 27%), mp 221°; ir: 3356 and 3212 (NH), 1663 (CO) cm^{-1}; ^1H nmr: δ 1.18 (3H, t, CH_3), 2.49 (2H, q, CH_2), 7.35-7.80 (14H, m, 2 x C_6H_5 and C_6H_4), 9.68 (1H, s, exchangeable NH), 11.07 (1H, s, exchangeable NH); ^{13}C nmr: δ 15.51 (q), 17.06 (t), 117.89 (s), 121.83 (s), 126.24 (d), 126.89 (d), 127.13 (d), 127.30 (d), 128.36 (d), 128.60 (d), 129.83 (s), 130.01 (s), 130.83 (s), 132.01 (s), 133.30 (s), 137.60 (s), 167.00 (s); ms: m/z (relative intensity) 400 (M^+, 83), 385 (15), 365 (16), 262 (31), 261 (99), 260 (52), 259 (37), 258 (10), 246 (32), 245 (80), 244 (52), 243 (37), 242 (16), 233 (36), 232 (99), 231 (24), 230 (21), 218 (19), 217 (26), 216 (11), 204 (13), 156 (15), 154 (13), 144 (22), 142 (18), 141 (98), 140 (39), 139 (99), 131 (15), 130 (28), 129 (48), 128 (51), 127 (30), 117 (16), 116 (33), 115 (98), 114 (16), 112 (19), 111 (99), 105 (30), 104 (99), 103 (24), 102 (26), 91 (26), 89 (30), 85 (13), 78 (23), 77 (100).

Anal. Calcd. for $C_{25}H_{21}ClN_2O$: C, 74.90; H, 5.28; N, 6.99. Found: C, 74.81; H, 5.33; N, 7.04.

The second product eluted was 3-benzamido-2,5-diphenyl-4-ethylpyrrole (**11**) (yield 10%); ir: 3410 and 3289 (NH), 1657 (CO) cm^{-1}; ^1H nmr: δ 1.11 (3H, t, CH_3), 2.32 (2H, q, CH_2), 7.26-8.03 (15H, m, 3 x C_6H_5), 9.67 (1H, s, exchangeable NH), 11.05 (1H, bs, exchangeable NH); ^{13}C nmr: δ 15.12 (q), 17.18 (t), 118.89 (s), 121.89 (s), 125.89 (d), 126.13 (d), 126.89 (d), 127.13 (s), 127.60 (d), 128.36 (d), 128.48 (d), 128.60 (d), 131.42 (s), 132.18 (s), 133.36 (s), 134.83 (s), 166.95 (s); ms: m/z (relative intensity): 366 (M^+, 33), 261 (23), 245 (9), 232 (11), 149 (16), 129 (23), 112 (10), 105 (15), 77 (10).

Anal. Calcd. for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.65. Found: C, 81.85; H, 6.00; N, 7.77.

Thermal Decomposition of the Pyrrolylbenzotriazinone **7**.

The benzotriazinone **7** (2 mmoles) was heated, in a silicon oil bath, at 250° until the gas evolution ceased (3 hours). After cooling, the residue was dissolved in dichloromethane and chromatographed using dichloromethane:ethyl acetate 95:5 as eluant. The only product eluted was 1,3-diphenyl-2*H*-pyrrolo[3,4-*c*]isoquinolin-5-one (**9**) (yield 25%), mp 260-262°; ir: 3380 and 3200 (NH),

1640 (CO) cm^{-1}; ^1H nmr: δ 7.41-7.63 (14H, m, ArH), 8.27 (1H, bs, exchangeable NH), 10.69 (1H, bs, exchangeable NH); ^{13}C nmr: δ 113.34 (s), 114.76 (s), 121.00 (d), 121.43 (s), 124.70 (d), 125.57 (d), 125.83 (d), 128.02 (d), 128.36 (d), 129.06 (d), 129.55 (d), 131.64 (d), 132.74 (d), 135.24 (s), 137.62 (s), 139.05 (s), 139.52 (s), 141.90 (s), 161.59 (s); ms: m/z (relative intensity): 336 (M^+, 100), 335 (4), 334 (4), 307 (5), 306 (6), 232 (10), 205 (4), 204 (9), 178 (6), 177 (4), 176 (4), 153 (4), 104 (5), 77 (12).

Anal. Calcd. for $C_{23}H_{16}N_2O$: C, 82.12; H, 4.79; N, 8.33. Found: C, 82.21; H, 4.83; N, 8.41.

Acknowledgements.

This work was in part supported by a Grant from C.N.R. (Rome) and from M.U.R.S.T.

REFERENCES AND NOTES

[1a] J. Pernak, J. Krysinski, and J. Jedraszczyk, *Pharm. Unserer Zeit.*, **15**, 47 (1986); *Chem. Abstr.*, **105**, 24164 (1986); [b] H. I. Hochman, K. C. Agrawal, and A. C. Sartorelli, *Biochem. Pharmacol.*, **21**, 3213 (1972).

[2a] R. M. Kanojia, O. W. Lever Jr., J. B. Press, L. Williams, H. M. Werblood, E. C. Giardino, R. Falotico, and A. J. Tobia, *J. Med. Chem.*, **32**, 990 (1989); [b] A. Morikawa, T. Sone, and T. Asano, *J. Med. Chem.*, **32**, 42 (1989); [c] A. Morikawa, T. Sone, and T. Asano, *J. Med. Chem.*, **32**, 46 (1989).

[3] L. Landriani, D. Barlocco, G. A. Pinna, M. P. Demontis, M. Miele, P. Enrico, and V. Anania, *Farmaco Ed. Sci.*, **44**, 1059 (1989).

[4] M. E. Bembenek, C. W. Abell, L. A. Chrisey, M. D. Rozwadowska, W. Gessner, and A. Brossi, *J. Med. Chem.*, **33**, 147 (1990).

[5a] M. Hagiwara, *Mie Med. J.*, **38**, 137 (1988); *Chem. Abstr.*, **110**, 53552 (1989); [b] M. Hagiwara, M. Inagaki, M. Watanable, M. Ito, K. Onoda, T. Tanaka, and H. Hidaka, *Mol. Pharmacol.*, **32**, 7 (1987).

[6] S. Klutchko, C. J. Blankley, R. W. Fleming, J. M. Hinkley, A. E. Werner, I. Nordin, A. Holmes, M. L. Hoefle, D. M. Cohen, A. D. Essenburg, and H. R. Kaplan, *J. Med. Chem.*, **29**, 1953 (1986).

[7] V. S. Georgiev, R. G. Van Inwegen, and P. Carlson, *Eur. J. Med. Chem.*, **25**, 375 (1990).

[8] G. Gardner and J. E. Semple, *J. Plant Growth Regul.*, **9**, 161 (1990); *Chem. Abstr.*, **114**, 2148 (1991).

[9] J. J. D'Amico, U.S. Patent 4097260 (1978); *Chem. Abstr.*, **89**, 192508 (1978).

[10a] Y. Arai and K. Enomoto, *Yakugaku Zasshi*, **88**, 1197 (1968); *Chem. Abstr.*, **70**, 27530 (1969); [b] Y. Arai and K. Enomoto, *Yakugaku Zasshi*, **88**, 44 (1968); *Chem. Abstr.*, **68**, 94351 (1968).

[11a] Y. C. Wu, Y. F. Liou, T. Sheng, C. H. Chen, J. J. Chang, and K. H. Lee, *Planta Medica*, **55**, 163 (1989); [b] S. Gjosal, S. Singh, Y. Kumar, and R. S. Srivastava, *Phytochemistry*, **28**, 611 (1989).

[12] G. Winters, N. Di Mola, M. Berti, and V. Arioli, *Farmaco Ed. Sci.*, **34**, 507 (1979).

[13] B. Lal and A. P. Bhaduri, *Indian J. Chem. Sect. B*, **15**, 359 (1977).

[14] W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **11**, 1031 (1972).

[15] A. Waldner, A. Roloff, and D. Bellus, European Patent 161221 (1985); *Chem. Abstr.*, **104**, 207246 (1986).

[16] A. Waldner, European Patent 172140 (1986); *Chem. Abstr.*, **105**, 24256 (1986).

[17] A. Waldner, *Helv. Chim. Acta*, **71**, 486 (1988).

[18] J. C. Tou, L. A. Shadoff, and R. H. Rigterink, *Org. Mass Spectrom.*, **2**, 355 (1969).

[19] C. Wunsche, G. Ege, E. Beisiegel, and T. Pasedach, *Tetrahedron*, **25**, 5869 (1969).

[20a] D. H. Hey, C. W. Rees, and A. R. Todd, *Chem. Ind. (London)*, 1332 (1962); [b] D. H. Hey, C. W. Rees, and A. R. Todd, *J. Chem. Soc. (C)*, 1028 (1968); [c] G. Ege, P. Arnold, E. Beisiegel, and I. Lehrer, *Liebigs Ann. Chem.*, 946 (1976); [d] A. J. Barker, T. McC. Paterson, R. K. Smalley, and H. Suschitzky, *J. Chem. Soc. Perkin Trans. 1*, 2203 (1979).

[21] M. S. Gibson, *J. Chem. Soc.*, 3539 (1963).

[22] A. J. Boulton and A. McKillop in Comprehensive Heterocyclic Chemistry, Vol **2**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, 1984, p 12.

[23] F. Angelico, *Rendiconti Accad. Lincei*, **14**, II, 167 (1905).