Pergamon

Tetrahedron, Vol. 53, No. 2, pp. 641-646, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)01025-3

A Novel Access to 2, 4-Substituted Quinolines from Acetylenic Ketones

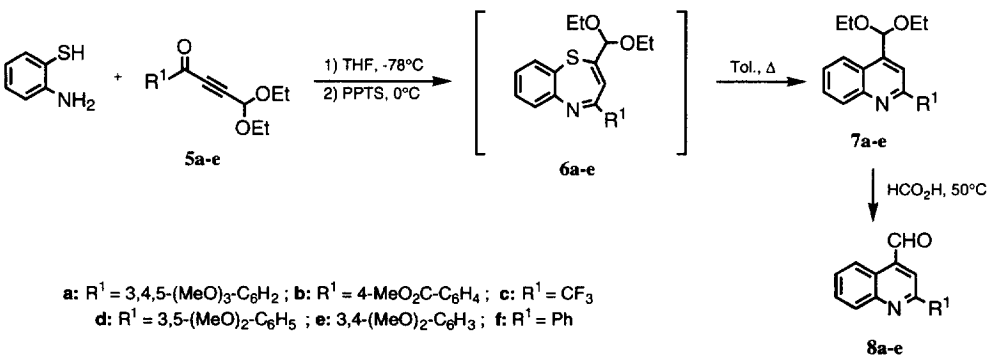
T. Masquelin, D. Obrecht*

F. Hoffmann-La Roche Ltd., Pharma Research
CH-4070 Basel, Switzerland

Abstract: 2, 4-Substituted quinolines of type **7** and **8** were synthesized starting from 2-amino thiophenol and acetylenic acetals **5** to yield various substituted benzo[b][1, 4] thiazepine intermediates of type **6**. Subsequent sulfur extrusion in refluxing toluene led to 2, 4-substituted quinoline acetals **7**, which were transformed into the corresponding 2-substituted quinoline-4-carbaldehydes **8** in good to excellent yields. Copyright © 1996 Elsevier Science Ltd

In recent years, significant attention has focused on the synthesis of quinolines and derivatives as many naturally occurring quinolines are known for their biological activity and specially designed quinolines have found many applications in the pharmaceutical field [1]. In the past, the preparation of the quinoline ring system was of major interest within the chemistry of fused five and six-membered heterocycles. The preparation of quinolines was accomplished using both classical and nonclassical approaches, such as for example: *a*) the general *Skraup synthesis* from aniline derivatives [2], b) the *Friedlaender quinoline synthesis* [3], c) the formation of 2-hydroxyquinolines from ß-ketoesters [4], d) the *Pfitzinger reaction* [5], e) reaction of *N*-arylnitrilium salts with acetylenes [6], f) photochemical and thermal transformations of triarylpyrimidin-2(1H)-ones [7]. Despite of all these approaches toward the quinoline skeleton, there is still room for further developments, especially with regard to parallel and combinatorial synthesis [8].

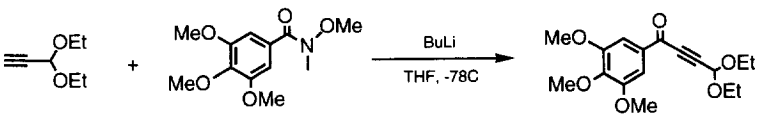
For all these reasons, we present in this paper a versatile general access to 2, 4-substituted quinolines of type **7** and **8**, based on the cyclocondensation reaction of 2-amino thiophenol with the corresponding acetylenic acetals of type **5** to give the substituted benzo[b][1, 4] thiazepines **6,** followed by sulfur extrusion and hydrolysis (**Scheme 1**). Acetylenic ketones **5** have been shown by our group to be highly versatile building blocks for the synthesis of 3-halofurans, flavones, styrylchromones [9], 3-halopyrroles [10] and 3-halothiophenes [11].



a: R^1 = 3,4,5-$(MeO)_3$-C_6H_2 ; **b:** R^1 = 4-MeO_2C-C_6H_4 ; **c:** $R^1 = CF_3$
d: R^1 = 3,5-$(MeO)_2$-C_6H_5 ; **e:** 3,4-$(MeO)_2$-C_6H_3 ; **f:** R^1 = Ph

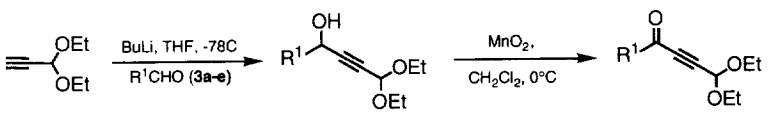
Scheme 1

The synthesis of the acetylenic acetals **5** was achieved in good yields starting from either *N*-methoxy-*N*-methylamide **2** (**Scheme 2**) [9] or from the corresponding aldehydes **3** (**Scheme 3**) [9]. They reacted smoothly with the acetylide obtained by treatment of the commercially available 3,3-diethoxyprop-1-yne **1** with BuLi in THF at -78°C [12].



1 **2** **5a**

Scheme 2



1 **4a-e** **5b-f**

Scheme 3

In cases where the aldehydes were commercially available, we preferred the two step procedure *via* the acetylenic alcohols **4** because of slightly better overall yields. Oxidation of the intermediate alcohols with MnO_2 in CH_2Cl_2 afforded the acetylenic ketones **5b-f** in good overall yields (**Table 1**).

Table 1 : Synthesis of Acetylenic Ketones **5a-e.**

	R^1	Method	Product	Yield[%]
2a	3,4,5-$(MeO)_3$-C_6H_2	A	**5a**	89
3a	4-MeO_2C- C_6H_4	B	**5b**	89
3b	CF_3	B	**5c**	77
3c	3,5-$(MeO)_2$- C_6H_3	B	**5d**	77
3d	3,4-$(MeO)_2$- C_6H_3	B	**5e**	78
3e	Ph	B	**5f**	89

Synthesis of the 2, 4-substituted quinolines started with reacting acetylenic ketones **5a-f** and 2-amino thiophenol in dry THF at -78°C, followed by acid-catalysed cyclisation at 0°C with PPTS to form the corresponding substituted benzo[b][1, 4] thiazepine intermediates of type **6**. Due to the fact, that after isolation the substituted benzo[b][1, 4] thiazepine intermediates **6** contained already some quinolines of type **7** (except in the case of **6f**, which was obtained in pure form) prompted us to directly move on to **7** by heating the crude intermediates **6** in refluxing toluene during a few hours (**Table 2**).

Table 2 : Synthesis of 2, 4-substituted quinolines **7**.

	R^1	Product	Yield[%]
5a	3,4,5-$(MeO)_3$-C_6H_2	**7a**	47
5b	4-MeO_2C- C_6H_4	**7b**	55
5c	CF_3	**7c**	41
5d	3,5-$(MeO)_2$- C_6H_3	**7d**	79
5e	3,4-$(MeO)_2$- C_6H_3	**7e**	65
5f	Ph	**7f**	64

After sulfur extrusion, treatment of **7** with formic acid at 50°C afforded the corresponding 2-substituted quinoline-4-carbaldehydes of type **8** in excellent yields (**Table 3**).

Table 3 : Synthesis of 2-substituted quinoline-4-carbaldehydes **8a-f.**

	R^1	Product	Yield[%]
7a	3,4,5-$(MeO)_3$-C_6H_2	**8a**	92
7b	4-MeO_2C- C_6H_4	**8b**	96
7c	CF_3	**8c**	69
7d	3,5-$(MeO)_2$- C_6H_3	**8d**	82
7e	3,4-$(MeO)_2$- C_6H_3	**8e**	76
7f	Ph	**8f**	85

The presented strategy allows us to rapidly synthesize regioselectively 2, 4-substituted quinolines of types **7** and **8** as shown in **Scheme 1**. This approach constitutes a novel and efficient synthesis towards 2, 4-substituted quinolines using the highly versatile acetylenic ketones of type **5**, in combination with a sulfur extrusion reaction of the intermediately formed benzo[b][1, 4] thiazepines **6**. Application towards the parallel and combinatorial synthesis of biologically interesting quinolines using this strategy will be reported in due course.

Experimental Part

All reactions which require air-or moisture sensitive reactants and solvents were carried out in oven- or flame-dried glassware under a positive pressure of dry Ar. Reaction solvents and liquid reagents were purified before use. Toluene was distilled under Ar, THF over Na with benzophenone ketyl as indicator. All other reactants were "reagent-grade" unless described otherwise. Anal. TLC : 2.5 x 10 cm precoated TLC plates, SiO_2 *60F-254*, layer thickness 0.25 mm (*E. Merck & Co.,* Darmstadt, Germany). Flash chromatography (FC) [13] : *E. Merck* SiO_2 60 (70-230 Mesh ASTM). M.p.: *Büchi-Smp-20* apparatus; uncorrected. IR : *Nicolet-7199 FT-IR* spectrometer; solids in KBr pellets, liquids as thin films; characteristic bands in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-AC-250* apparatus, at 250 MHz; in DMSO or CDCl3 ; TMS as internal standard; chemical shift of signal centers and ranges in ppm (δ), *J* in Hz. MS: *Finnigan MS9-AEI* or *Mat90* ; m/z (rel.-%).

Method A : A mixture of 1.29 mmol of acetylenic ketone of type **5** and 1.42 mmol of 2-amino thiophenol in tetrahydrofuran (THF, 4ml) was stirred for 2h at -78°C. The reaction was slowly warmed up to 0°C and 20% mol of pyridinium *p*-toluenesulfonate (PPTS) was added. After stirring 1h at 0°C, the mixture was quenched with a phosphate buffer solution (pH=7) and extracted with EtOAc (2x50ml). The combined organic layers were washed with H_2O (2x50ml), sat. brine (25ml), dried (Na_2SO_4) and the solvents evaporated. The residue

was chromatographed on SiO_2 with CH_2Cl_2/EtOAc (20 : 1). The benzo[b][1, 4]thiazepine intermediates of type **6** (2.7mmol) were immediately dissolved under argon in toluene (10ml) and refluxed for 2h. The mixture was cooled, the solvent evaporated under reduced pressure, and the residue was chromatographed on SiO_2 with hexane/EtOAc (10 : 1).

Method B : The quinoline of type **7** (4.8 mmol) were dissolved in formic acid (14ml) and stirred at 50°C for several hours. The reaction mixture was cooled to r.t., the solvent was evaporated and the residues chromatographed on SiO_2 with hexane/EtOAc (95 : 5).

2-Diethoxymethyl-4-phenyl-benzo[b][1, 4] thiazepine (6f) : A solution of 0.3g (1.29 mmol) of **5f** in THF(4ml) was treated with 0.18g (1.42 mmol) of 2-amino thiophenol and stirred for 2h at -78°C. The reaction was slowly warmed up to 0°C and 20% mol of pyridinium *p*-toluenesulfonate (PPTS) was added. After stirring 1h at 0°C, the mixture was quenched with a phosphate buffer solution (pH=7) and extracted with EtOAc (2x50ml). The combined organic layers were washed with H_2O (2x50ml), sat. brine (25ml), dried (Na_2SO_4) and the solvents evaporated. The residue was chromatographed on SiO_2 with CH_2Cl_2/EtOAc (20 : 1) to yield 0.389g (89%) of **6f** as a pale yellow oil after FC. IR (Nujol) : 3058m, 2975s, 2879m, 1627s, 1600s, 1573s, 1480w, 1127s, 1059s, 766s, 693s. ^{1}H-NMR ($CDCl_3$, 250 MHz) : 8.0-7.95 (m, 2 arom. H); 7.5-7.45 (m, 3 arom. H); 7.35-7.3 (m, 3 arom. H); 7.2-7.15 (m, 1 arom. H); 6.85 (m, C=CH); 5.02 (s, $CH(OEt)_2$); 3.65-3.55 (m, 4 aliph. H) ; 1.3-1.2 (m, 6 aliph. H). ^{13}C-NMR ($CDCl_3$, 400 MHz) : 15.26 (2q); 61.9 (2t); 101.1 (d); 126.4 (2d); 126.5 (d), 127.7 (2d); 128.5 (2d); 128.8 (d); 130.8 (d); 132.6 (d); 138.9 (s); 148.9 (s); 149.8 (s); 164.9 (s). MS : 339 (M^+, 10), 307 (24), 262 (30), 234 (24), 206 (28), 103 (100), 75 (60), 47 (60).

4-Diethoxymethyl-2-(3, 4, 5-trimethoxy-phenyl) quinoline (7a) : 3.0g (9.3 mmol) of **5a** was treated according to *Method* A with 1.09g (10.2 mmol) of 2-amino thiophenol : 1.74g (47%) of **7a** as a pale yellow oil after FC. IR (Nujol) : 2974m, 1755m, 1602m, 1507m, 1237m, 1129s, 1009s, 767m. ^{1}H-NMR (DMSO(D_6), 250 MHz) : 8.4-8.3 (m, 1 arom. H); 8.15-8.1 (m, 2 arom. H); 7.85-7.8 (m, 1 arom. H); 7.65-7.6 (m, 1 arom. H); 7.53 (s, 2 arom. H); 6.05 (s, $CH(OEt)_2$); 3.95 (s, 2 MeO); 3.75 (s, MeO); 3.7-3.3 (m, 4 aliph. H); 1.25-1.15 (t, J=7. 3, 6 aliph. H). MS : 398 ($(M+H)^+$, 100).

4-(4-Diethoxymethyl-quinolin-2-yl) benzoic acid methyl ester (7b) : 3.0g (10.3 mmol) of **5b** was treated according to *Method* A with 1.46g (11.3 mmol) of 2-amino thiophenol : 2.08g (55%) of **7b** as a yellow cristalline product after FC. IR (Nujol) : 3434m, 2977m, 1721s, 1599w, 1437m, 1278s,1132s, 1111s, 774s. ^{1}H-NMR (DMSO(D_6), 250 MHz) : 8.45-8.3 (m, 3 arom. H); 8.25 (s, 1 arom. H); 8.2-8.1 (m, 3 arom. H); 7.85-7.8 (m, 1 arom. H); 7.7-7.6 (m, 1 arom. H); 6.15 (s, $CH(OEt)_2$); 3.9 (s, MeO); 3.7-3.6 (m, 4 aliph. H); 1.25-1.15 (t, J=7. 3, 6 aliph. H). MS : 365 (M^+, 85), 322 (20), 320 (100), 292 (60), 264 (55), 204 (25), 103 (50), 75 (20), 47 (15).

4-Diethoxymethyl-2-trifluoromethyl-quinoline (7c) : 3.0g (13.1 mmol) of **5c** was treated according to *Method* A with 1.8g (14.4 mmol) of 2-amino thiophenol : 1.65g (41%) of **7c** as a pale yellow oil after FC. IR (Nujol) : 3451m, 2989s, 2891m, 1615w, 1467m, 1350s,1179s, 1132s, 759s. ^{1}H-NMR (DMSO(D_6), 250 MHz) : 8.5-8.4 (m, 1 arom. H); 8.25-8.2 (m, 1 arom. H); 8.0-7.8 (m, 3 arom. H); 6.25 (s, $CH(OEt)_2$); 3.7-3.6 (m, 4 aliph. H); 1.3-1.25 (t, J=7. 3, 6 aliph. H). MS : 299 (M^+, 5), 255 (85), 254 (90), 226 (100), 198 (15), 178 (30), 128 (20), 103 (15), 75 (10). Anal. calc. for $C_{15}H_{16}NO_2F_3$: C 60.20, H 5.39, N 4.68; found : C 59.91, H 5.36, N 4.77.

4-Diethoxymethyl-2-(3, 5-dimethoxy-phenyl) quinoline (7d) : 2.1g (7.18 mmol) of **5d** was treated according to *Method* A with 0.98g (7.89 mmol) of 2-amino thiophenol : 2.08g (79%) of **7d** as a pale yellow oil product after FC. IR (Nujol) : 2975m, 1599s, 1510w, 1274m, 1155s, 1063s, 759m. ^{1}H-NMR (DMSO(D_6), 250 MHz) : 8.4-8.3 (m, 1 arom. H); 8.15-8.1 (m, 2 arom. H); 7.85-7.75 (m, 1 arom. H); 76-7.55 (m, 1 arom. H); 7.40-7.35 (m, 2 arom. H); 6.70-6.65 (m, 1 arom. H); 6.08 (s, $CH(OEt)_2$); 3.87 (s, 2 MeO); 3.7-3.6 (m, 4 aliph. H); 120-1.15 (t, J=7. 3, 6 aliph. H). MS : 367 (M^+, 100), 322 (35), 294 (25), 266 (20).

4-Diethoxymethyl-2-(3, 4-dimethoxy-phenyl) quinoline (7e) : 2.1g (7.18 mmol) of **5e** was treated according to *Method A* with 0.98g (7.89 mmol) of 2-amino thiophenol : 1.7g (65%) of **7e** as a pale yellow oil after FC. IR (Nujol) : 2975m, 1602m, 1498s, 1274m, 1177m, 1023m, 762m. ^{1}H-NMR (DMSO(D_6), 250 MHz) : 8.3-8.25 (m, 1 arom. H); 8.1-8.05 (m, 2 arom. H); 7.8-7.75 (m, 1 arom. H); 7.65-7.6 (m, 1 arom. H); 7.4-7.35 (m, 1 arom. H); 7.15-7.1 (m, 2 arom. H); 6.1 (s, $CH(OEt)_2$); 3.8-3.75 (2s, 2 MeO); 3.7-3.6 (m, 4 aliph. H); 1.2-1.15 (t, J=7. 3, 6 aliph. H). MS : 368 ($(M+H)^+$, 100).

4-Diethoxymethyl-2-phenyl-quinoline (7f) : 0.30g (1.29 mmol) of **5f** was treated according to *Method* A with 0.17g (1.42 mmol) of 2-amino thiophenol : 0.257g (64%) of **7f** as a yellow oil after FC : IR (Nujol) : 3432w, 2974m, 1599m, 1495w, 1123s, 1051s, 770s, 694s. ^{1}H-NMR (DMSO(D_6), 250 MHz) : 8.25-8.15 (m, 5 arom. H); 7.75-7.7 (m, 1 arom. H); 7.6-7.5 (m, 4 arom. H); 6.08 (s, $CH(OEt)_2$); 3.7-3.6 (q, J=7.2, 4 aliph. H); 1.3-1.25 (t, J=7. 3 aliph. H). MS : 307 (M^+, 68), 263 (40), 262 (100), 234 (56), 207 (10), 106 (64), 204 (52), 203 (10), 128 (24), 103 (82), 101 (14), 77 (12), 75 (60), 51 (10), 47 (46).

2-(3, 4, 5-Trimethoxy-phenyl) quinoline-4-carbaldehyde (8a) : 1.95g (4.89 mmol) of **7a** was treated according to *Method B* : 1.45g (92%) of **8a** as a pale yellow powder after FC. Mp : 124-125°C. IR (KBr) : 3442s, 2820w, 1692s, 1593m, 1595s, 1504s, 1224s, 1129s, 1005s, 761s. ^{1}H-NMR ($CDCl_3$, 250 MHz) : 10.6 (s, CHO); 9.0-8.95 (m, 1 arom. H); 8.3-8.25 (m, 1 arom. H); 8.22 (s, 1 arom. H) 7.85-7,8 (m, 1 arom. H); 7.75-7.7 (m, 1 arom. H); 7.46 (s, 2 arom. H); 4.03 (s, 2 MeO); 3.94 (s, MeO). MS : 323 (M^+, 100), 308 (40), 250 (20). Anal. calc. for $C_{19}H_{17}NO_4$: C 70.51, H 5.39, N 4.28; found : C 70.23, H 5.25, N 4.12.

4-(4-Formyl-quinolin-2-yl) benzoic acid methyl ester (8b) : 2.02g (6.98 mmol) of **7b** was treated according to *Method B*: 1.54g (96%) of **8b** as a white powder after FC. Mp : 157-158°C. IR (KBr) : 3434m, 1711s, 1699s, 1594w, 1437w, 1286s, 1108m, 778s. ^{1}H-NMR ($CDCl_3$, 250 MHz) : 10.6 (s, CHO); 9.0-8.95 (m, 1 arom. H); 8.35-8.2 (m, 6 arom. H); 7.9-7,8 (m, 1 arom. H); 7.8-7.7 (m, 1 arom. H); 3.98 (s, MeO). MS : 291 (M^+, 100), 260 (90), 232 (20), 204 (20). Anal. calc. for $C_{18}H_{13}NO_3$: C 74.22, H 4.50, N 4.81; found : C 73.91, H 4.46, N 4.96.

2-Trifluoromethyl-quinoline-4-carbaldehyde (8c) : 1.65g (7.19 mmol) of **7c** was treated according to *Method B* : 1.06g (69%) of **8c** as a brown powder after FC. Mp : 98-99°C. IR (KBr) : 3434m, 2790w, 1705s, 1598w, 1472w, 1155s, 1055m, 774s. ^{1}H-NMR ($CDCl_3$, 250 MHz) : 10.6 (s, CHO); 9.1-9.05 (m, 1 arom. H); 8.4-8.3 (m, 1 arom. H); 8.14 (s, 1 arom. H); 7.95-7,85 (m, 2 arom. H). MS : 225 (M^+, 100), 197 (40), 196 (30), 128 (35), 101 (15). Anal. calc. for $C_{11}H_6NOF_3$: C 58.68, H 2.69, N 6.22; found : C 58.49, H 2.83, N 6.34.

2-(3, 5-Dimethoxy-phenyl) quinoline-4-carbaldehyde (8d) : 2.08g (5.48 mmol) of **7d** was treated according to *Method B* : 1.31g (82%) of **8d** as a brownish powder after FC. Mp : 105-106°C. IR (KBr) : 3441m, 2875w, 1705s, 1597s, 1550m, 1212m, 1154s 1048m, 759s. ^{1}H-NMR ($CDCl_3$, 250 MHz) : 10.57 (s, CHO); 9.0-8.95 (m, 1 arom. H); 8.3-8.25 (m, 1 arom. H); 8.21 (s, 1 arom. H); 7.85-7,8 (m, 1 arom. H); 7.75-7.65 (m, 1 arom. H); 7.4-7.35 (m, 2 arom. H); 6.65-6.60 (m, 1 arom. H); 3.92 (s, 2MeO). MS : 293 (M^+, 100), 263 (35). Anal. calc. for $C_{18}H_{15}NO_3$: C 73.71, H 5.15, N 4.78; found : C 7.43, H 5.41, N 4.63.

2-(3, 4-Dimethoxy-phenyl) quinoline-4-carbaldehyde (8e) : 1.72g (4.5 mmol) of **7e** was treated according to *Method B* : 1.05g (76%) of **8e** as a brownish powder after FC. Mp : 84-86°C. IR (KBr) : 3439m, 2875w, 1695s, 1596m, 1498s, 1266s, 1149m, 1025m, 764s. ^{1}H-NMR ($CDCl_3$, 250 MHz) : 10.5 (s, CHO); 9.1-9.0 (m, 1 arom. H); 8.39 (s, 1 arom. H); 8.3-8.25 (m, 1 arom. H); 7.85-7,65 (m, 2 arom. H); 7.6-7.55 (m, 1 arom. H); 7.05-7.0 (m, 2 arom. H); 3.87 (s, MeO); 3.86 (s, MeO). MS : 293 (M^+, 100), 276 (25), 264 (50), 236 (15). Anal. calc. for $C_{18}H_{15}NO_3$: C 73.71, H 5.15, N 4.78; found : C 7.36, H 5.02, N 4.88.

2-Phenyl-quinoline-4-carbaldehyde (8f) : 1.19g (3.87mmol) of **7f** was treated according to *Method B* : 0.73g (85%) of **8f** as a white powder after FC. Mp : 66-67°C. IR (KBr) : 3429m, 3080w, 2775w, 1707s, 1593m, 1546m, 1493m, 1332s, 1049m, 767s, 686s. ^{1}H-NMR ($CDCl_3$, 250 MHz) : 10.5 (s, CHO); 9.0-8.95 (m, 1 arom. H); 8.25-8.2 (m, 4 arom. H); 7.85-7,8 (m, 1 arom. H); 7.75-7.7 (m, 1 arom. H); 7.6-7.5 (m, 3 arom. H). MS : 233 (M^+, 100), 204 (80), 203 (10). Anal. calc. for $C_{16}H_{11}NO$: C 81.43, H 5.01, N 6.33; found : C 81.43, H 4.81, N 6.16.

Acknowledgements: We gratefully thank our colleages from *F. Hoffmann-La Roche AG* for analytical support and Profs. Drs *K. Müller, H.J. Hansen, J. Baldwin, F. Diederich,* and *A. Vasella* for fruitful discussions.

References

1. Campbell, N. " Rodd's Chemistry of Carbon Compounds ", ed. by E. H. Rodd, Elsevier Scientific Publishing Company, Amsterdam. **1976**, Vol. IVF, 231.
2 Skraup, Z. H. *Ber., 1880, 13*, 2086
3 Friedlaender, P., *Ber.* **1882**, *41*, 4271.

4 Knorr, L. *Ann.* **1886**, *236*, 69.
5 Pfitzinger, W. *J. Prakt. Chem.* **1886**, *33*, 100.
6 Al-Talib, M. ; Jochims, J. C. ; Wang, Q. ; Atef, A. ; Abd El-Hamid, I. *Synthesis*, **1992**, 875.
7 Nishio, T. ; Katahira, K. ; Omote, Y. *Tetrahedron Lett.* **1980**, *21*, 2825.
8 Hermkens, P. H. H. ; Ottenheijm, H. C. J. ; Rees, D. *Tetrahedron*, **1996**, *52*, 4527.
9 Obrecht, D. ; Weiss, B. *Helv. Chim. Acta* **1989**, *72*, 117.
10 Masquelin, T. ; Obrecht, D. *Synthesis* **1995,** 276.
11 Masquelin, T. ; Obrecht, D. *Tetrahedron Lett.* **1994,** 9387.
12 Barbot, F. ; Miginiac, P. *Tetrahedron Lett.* **1979**, 4825.
13 Still, W. C. ; Kahn, M. ; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(*Received in Germany* 26 *October* 1996; *accepted* 31 *October* 1996)