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IMPROVED PROCEDURES FOR LARGE SCALE PREPARATION OF 6- AND 7-OXY-SUBSTITUTED ISOQUINOLINES AND A CONVENIENT WORK-UP PROTOCOL FOR TITANIUM SUPPORTED REACTIONS

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Abstract: Improved procedures for large scale preparation of oxy-substituted isoquinolines are reported. Moreover, a simple and convenient protocol for alkaline work-up of titanium containing reaction mixtures is given, which is expected to be of general interest even for reactions on a technical scale.

Since isoquinolines are valuable building blocks in drug[1] and dye[2] research, a vast array of synthetic methods covering various kinds of substitution patterns are known[3]. As part of our research program we recently required large quantities of oxy-substituted isoquinolines. Hence, we looked for well-suited preparation methods with special focus on scale up feasibility. Oxy-substituted isoquinolines are commonly prepared as depicted in Scheme 1. A benzaldehyde derivative and an aminoacetaldehyde acetal are condensed to give the corresponding Schiff base,

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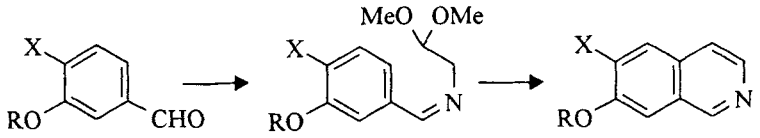


1a (R=Me, X=H) **2a** (R=Me, X=H) **3a** (R=Me, X=H)
1b (R=Bz, X=H) **2b** (R=Bz, X=H) **3b** (R=H, X=H)
1c (R=Me, X=OH) **2c** (R=Me, X=OH) **3c** (R=Me, X=OH)

SCHEME 1

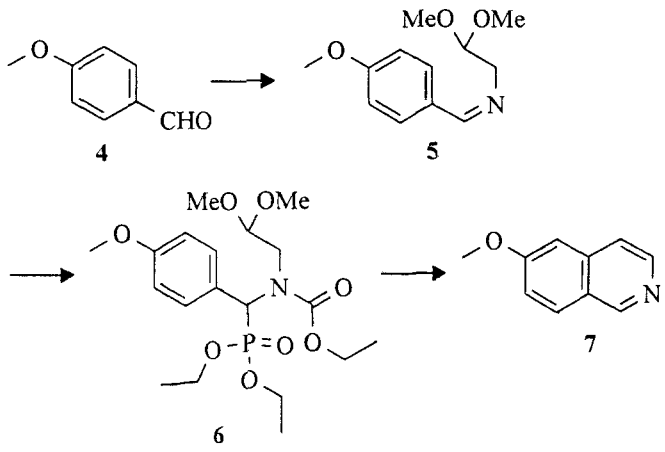
which undergoes intramolecular cyclization under acidic conditions (Pomeranz-Fritsch cyclization).

A modified procedure for the synthesis of 7-oxy-substituted isoquinolines using BF_3-AcOH in trifluoroacetic anhydride as cyclization reagent was described by Bevis and co-workers.[4] The mild conditions used in this protocol led us to apply this method to the synthesis of 7-methoxy-isoquinoline (**3a**) on multigram scale. In order to avoid large quantities of fluorinated waste we considerably reduced the amount of boron trifluoride and trifluoroacetic anhydride while toluene was used as solvent. This resulted in a convenient one-pot procedure affording **3a** with an improved overall yield of 84% (for details see experimental part). The methoxy group was not attacked under these conditions. In contrast, when 3-benzyloxy-benzaldehyde was used as starting material, a simultaneous cleavage of the benzyl ether occured to give isoquinolin-7-ol (**3b**, overall yield: 73%). To our knowledge this compound has so far solely been synthesized following the ancient procedures by Fritsch[5] and Woodward[6], which suffer from low reproducability. Moreover, a

phenolic hydroxy substituent is tolerated in the cyclization process. When vanillin was used as starting aldehyde the previously unknown 7-methoxy-isoquinolin-6-ol (**3c**) was obtained in an overall yield of 61%.

Attempts to apply this procedure to the synthesis of 6-methoxy-isoquinoline (**7**) failed due to the hindered cyclization of the intermediate Schiff base lacking an activating m-alkoxy-substituent. A literature search[7] revealed only three references for the preparation of said compound, two of which[8,9] requiring several reaction steps and partly harsh conditions. The third one[10] which is, again, based on a Pomeranz-Fritsch type conversion, is depicted in Scheme 2. The p-methoxy-benzaldehyde related Schiff base (**5**) is converted into its carbamate-phosphonate analogue (**6**), which undergoes titanium mediated intramolecular cyclization in the absence of an activating substituent.

In principal, this method works well. However, the published work-up procedure proved to be unsuitable for large scale preparations since the insoluble titanium dioxide formed upon alkaline hydrolysis plugs the pores of common suction filters and therefore impedes its separation. In order to avoid the precipitation of TiO_2 we masked the titanium species in the reaction mixture as soluble chelate complexes upon treatment with aqueous sodium potassium tartrate solution prior to alkaline work-up. Following this simplified procedure 6-methoxy-isoquinoline (**7**) was obtained in an improved overall yield of 84%. The use of sodium potassium tartrate in a twofold excess referring to the amount of $TiCl_4$ is essential (for details see experimental part).



SCHEME 2

In conclusion we have provided an improved procedure for the preparation of 6-methoxy-isoquinoline (7), which is now readily available on a multigram scale in good yields. The improved method is based on a simplified work-up procedure for titanium containing reaction mixtures, which avoids precipitation of titanium dioxide upon alkaline hydrolysis by formation of soluble titanium chelate complexes. We expect this protocol to be of general interest whenever titanium mediated reactions have to be worked up under alkaline conditions. Moreover, improved procedures for large scale syntheses of 7-methoxy-isoquinoline (**3a**) and isoquinolin-7-ol (**3b**) were presented. The latter protocol was also applied to a multigram synthesis of the previously unknown 7-methoxy-isoquinolin-6-ol (**3c**).

Experimental Section:

Melting points were determined on a Büchi model 530 apparatus and are

uncorrected. NMR spectra were obtained on a Bruker- AC 250 spectrometer (chemical shifts downfield from TMS as internal standard). Mass spectral data were collected on a Finnigan MAT 312 mass spectrometer (Micro PDP-11 computer, Finnigan program SS300).

7-Methoxy-isoquinoline (3a). Aminoacetaldehyde dimethyl acetal (79 g; 0.75 mol) was added to a solution of 3-methoxy-benzaldehyde (68 g; 0.50 mol) in 600 ml of toluene. The mixture was refluxed for 5 h using a Dean-Stark trap and subsequently cooled to 5°C. Under nitrogen trifluoroacetic acid anhydride (209 ml; 1.50 mol) and boron trifluoride etherate (185 ml; 1.50 mol) were added in succession at such a rate, that the internal temperature was kept below 10°C. After stirring for 3 days at room temperature the reaction was poured on ice, 2 N HCl (250 ml) was added and the organic layer extracted with 1 N HCl. The pH value of the combined aqueous extracts was adjusted to pH 9 by adding concentrated aqueous ammonia. Extraction with ethyl acetate, followed by drying and removal of the solvent in vacuo gave 67 g (84%) of the title compound as a light yellow oil. EI-MS: 159 (M^+); ^{1}H-NMR ($CDCl_3$): δ = 3.92 (s, 3H), 7.20 (d, 1H), 7.33 (m, 1H), 7.56 (d, 1H), 7.70 (d, 1H), 8.41 (d, 1H), 9.15 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ = 55.4, 104.6, 120.2, 123.6, 128.0, 129.8, 131.4, 141.2, 151.0, 158.4; anal. calcd for $C_{10}H_9NO$: C 75.45, H 5.70, N 8.80; found: C 75.33, H 5.71, N 8.95.

Isoquinolin-7-ol (3b). Aminoacetaldehyde dimethyl acetal (79 g; 0.75 mol) was added to 3-benzyloxy-benzaldehyde (0.50 mol, 106 g) in 1100 ml of toluene and refluxed for 6 h using a Dean-Stark trap. After cooling to 5°C trifluoracetic acid

anhydride (212 ml; 1.50 mol) and boron trifluoride etherate (185 ml; 1.50 mol) were added in succession under nitrogen at such a rate, that the internal temperature was kept below 10°C. After stirring for 5 days at room temperature the precipitated material was separated by filtration, washed several times with diethyl ether and dissolved in 750 ml of water. The pH value was adjusted to pH 9 by adding concentrated aqueous ammonia and the precipitated product separated by filtration, followed by washing with diethyl ether and drying in vacuo. Yield: 53 g (73%); light yellow solid; mp 228-230°C; EI-MS: 145 (M^+); ^{1}H-NMR ([D_6]DMSO): δ = 7.35 (s, 1H), 7.37 (m, 1H), 7.72 (d, 1H), 7.83 (d, 1H), 8.30 (d, 1H), 9.12 (s, 1H), 10.25 (s, 1H); ^{13}C-NMR ([D_6]DMSO): δ = 107.8, 120.0, 123.2, 128.1, 129.7, 129.9, 139.9, 150.4, 156.3; anal. calcd for C_9H_7NO: C 74.47, H 4.86, N 9.65; found: C 74.39, H 4.85, N 9.77.

7-Methoxy-isoquinolin-6-ol (3c). Aminoacetaldehyde dimethyl acetal (32 g; 0.30 mol) was added to a solution of vanillin (4-hydroxy-3-methoxy-benzaldehyde; 30 g; 0.20 mol) in 500 ml of toluene. The mixture was refluxed for 5 h using a Dean-Stark trap and subsequently cooled to 5°C. Under nitrogen trifluoroacetic acid anhydride (84 ml; 0.60 mol) and boron trifluoride etherate (74 ml; 0.60 mol) were added in succession at such a rate, that the internal temperature was kept below 10°C. After stirring for 3 days at room temperature the reaction mixture was poured on ice. The organic layer was discarded. Concentrated aqueous ammonia was added to the aqueous layer to adjust pH 9 followed by addition of sodium chloride and extraction of the resulting saturated solution with butanol. The solvent

was removed in vacuo and the remaining solid was washed with diethyl ether to afford 21 g (61%) of the title compound as a light brownish solid; mp 198-200°C; EI-MS: 175 (M^+); ^{1}H-NMR ([D_6]DMSO): δ = 3.97 (s, 3H), 7.00 (s, br, 1H), 7.19 (s, 1H), 7.46 (s, 1H), 7.55 (d, 1H), 8.22 (d, 1H), 9.03 (s, 1H); ^{13}C-NMR ([D_6]DMSO): δ = 55.6, 105.9, 107.7, 118.7, 123.9, 132.6, 139.9, 148.8, 150.0, 151.7; anal. calcd for $C_{10}H_9NO_2$ C 68.56, H 5.18, N 8.00; found: C 68.33, H 5.31, N 8.11.

6-Methoxy-isoquinoline (7). Aminoacetaldehyde dimethyl acetal (63 g; 0.60 mol) was added to 4-methoxy-benzaldehyde (54 g; 0.40 mol) in 1000 ml of toluene. The mixture was refluxed for 16 h using a Dean-Stark trap, the toluene distilled off and the residue was redissolved in 1000 ml of tetrahydrofuran. Ethyl chloroformate (38 ml; 0.40 mol) and triethylphosphite (84 ml; 0.48 mol) were added succesively at 0°C and the mixture stirred overnight at ambient temperature, followed by evaporation of the volatiles. Dichloromethane (1000 ml) and $TiCl_4$ (176 ml; 1.60 mol) were added and the mixture refluxed for 16 h. The mixture was poured on ice, the aqueous layer was washed with dichloromethane twice and subsequently poured into a solution of sodium potassium tartrate tetrahydrate (900 g; 3.20 mol) in 1500 ml of water. Concentrated aqueous ammonia was added (pH 9) and the aqueous solution extracted with dichloromethane several times. Drying of the combined organic extracts (Na_2SO_4) followed by removal of the solvent in vacuo afforded pure 6-methoxy-isoquinoline (54 g; 84%) as a light yellow oil. EI-MS: 159 (M^+); ^{1}H-NMR ([D_6]DMSO): δ = 3.95 (s, 3H), 7.30 (m, 2H), 7.71 (d, 1H),

8.01 (d, 1H), 8.42 (d, 1H), 9.16 (s, 1H); ^{13}C-NMR ([D$_6$]DMSO): δ = 55.4, 104.3, 119.6, 120.1, 124.1, 137.2, 143.3, 151.4, 160.4, 172.0; anal. calcd for $C_{10}H_9NO$: C 75.45, H 5.70, N 8.80; found: C 75.51, H 5.77, N 8.69.

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