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Solid-Phase Synthesis of *N*-Hydroxyindoles and Benzo[*c*]isoxazoles by C-Arylation of Substituted Acetonitriles and 1,3-Dicarbonyl Compounds with Polystyrene-bound Aryl Fluorides

Henrik Stephensen and Florencio Zaragoza*

Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark

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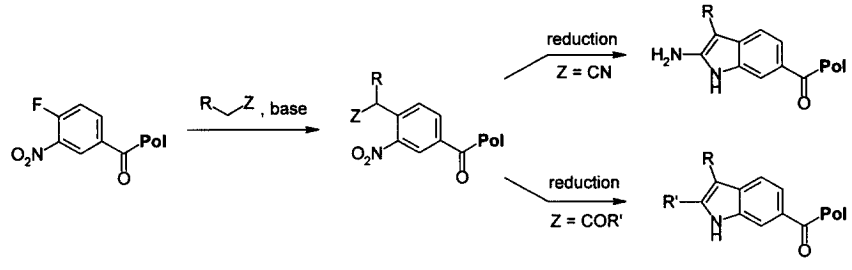
Abstract: The reaction of different carbon nucleophiles with resin-bound 4-fluoro-3-nitrobenzoic acid and the chemistry of the resulting products has been investigated. Treatment of Wang resin bound 4-fluoro-3-nitrobenzoic acid with 1,3-dicarbonyl compounds or acceptor-substituted acetonitriles, followed by reduction of the nitro group and cleavage from the support, led to substituted 1-hydroxy-6-indolecarboxylic acids. Treatment of polystyrene-bound 4-fluoro-3-nitrobenzoic acid amides with arylacetonitriles led to 4-aroyl-3-nitrobenzoic acid derivatives, which upon reduction with tin(II) chloride yielded benzo[*c*]isoxazoles.

Keywords: Solid-phase synthesis, indoles, C-arylation, benzisoxazoles

Substituted indoles are an important class of compounds with a broad spectrum of biological activities. Synthetic sequences which enable the parallel automated synthesis of indole derivatives are therefore of interest for the preparation of compound libraries for drug discovery.

As part of a program directed towards the development of synthetic methodology for the automated production of drug-like compounds[1] we have investigated the reactions of polystyrene-bound 4-fluoro-3-nitrobenzoic acid derivatives with C,H-acidic compounds and the reduction with tin(II) chloride of the resulting products. Our aim was to realize on cross-linked polystyrene the indole synthesis sketched in Scheme 1.[2]



Scheme 1.

* Corresponding author. Tel: (+45) 4443 4828; Fax: (+45) 4466 3450; e-mail: flo@novo.dk

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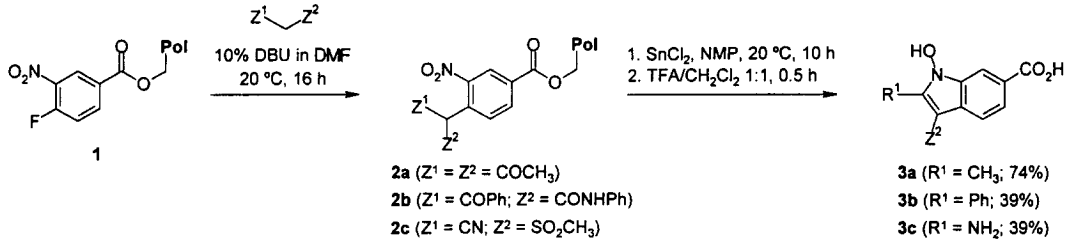
We found that Wang resin bound 4-fluoro-3-nitrobenzoic acid **1**[3] smoothly reacts with 1,3-dicarbonyl compounds or acceptor-substituted acetonitriles at room temperature in the presence of DBU or $KN(SiMe_3)_2$ to yield intermediates **2** (Scheme 2).[4] Treatment of these intermediates **2** with tin(II) chloride dihydrate in 1-methyl-2-pyrrolidinone, followed by cleavage from the support led to the formation of *N*-hydroxyindoles **3**.[2g,5] Reductive cleavage of the N–O bond was attempted with titanium(III) chloride[6] and sodium borohydride/copper(II) acetylacetonate,[7] but did not proceed in our hands with either of these reagents. Currently further reductants are being evaluated.

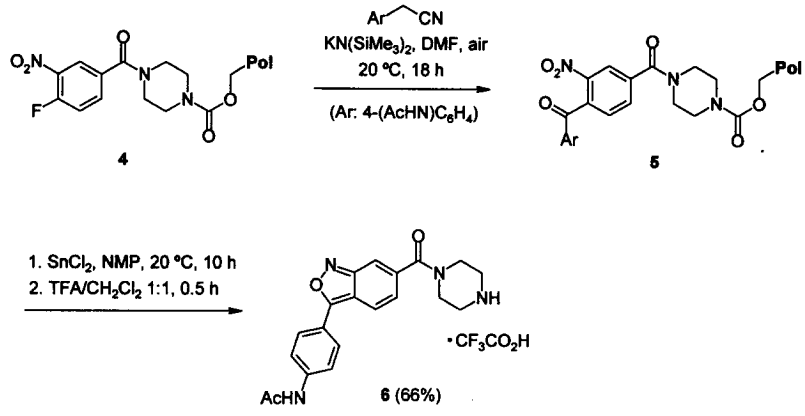


Scheme 2. **Pol**: 1% Cross-linked polystyrene with Wang linker. Yields (based on the loading of **1**) refer to analytically pure products.

We then turned our attention to less acidic carbon nucleophiles, namely arylacetonitriles. To avoid premature cleavage from the support, experiments with strong nucleophiles were conducted with support-bound piperazine amide **4** (Scheme 3). Arylacetonitriles generally required a strong base, such as potassium bis(trimethylsilyl)amide or potassium *tert*-amylate, to undergo reaction with the resin-bound aryl fluoride. To our surprise, reaction of 4-(acetylamino)phenylacetonitrile with aryl fluoride **4** did not yield the expected 1,1-diarylacetonitrile but, by oxidative decyanation of this intermediate,[8,9] the benzophenone **5** (Scheme 3).[4] Oxidative decyanation could only be suppressed in part by shortening the reaction time to 10 min, and quenching with dilute acetic acid in methanol. Reduction of benzophenone **5** with tin(II) chloride, followed by acidolytic cleavage from the support, led to the clean formation of benzisoxazole **6**.[10,11] Hence, as in the reduction of intermediates **2** with tin(II) chloride, only a partial reduction of the nitro group to a hydroxylamine derivative occurred. This result was unexpected as, with similar polystyrene-bound substrates, tin(II) chloride in polar aprotic solvents generally leads to complete reduction.[1a,3] We are currently investigating further synthetic applications of benzophenones **5** and benzisoxazoles **6**.

Acknowledgment

We thank Vibeke Rode for recording LCMS spectra and Flemming Gundertofte for the elemental analyses.



Scheme 3. **Pol**: 1% Cross-linked polystyrene with Wang linker.

References and Notes

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4. The structure of intermediates **2** and **5** was determined by cleavage from the support (trifluoroacetic acid/dichloromethane 1:1, 20 °C, 0.5 h) and full characterization of the resulting products. All new products were analyzed by LCMS, HPLC, ^{1}H NMR, and elemental analysis. The loading of **1** and **4** was determined by cleavage (as above) and yield-determination by ^{1}H NMR with an internal reference. Yields of products **3** and **6** were calculated on the basis of this loading.
5. Typical procedure for the preparation of 1-hydroxyindoles **3**: 3-Acetyl-1-hydroxy-2-methylindol-6-carboxylic acid (**3a**). DMF (4 mL), 2,4-pentanedione (0.31 mL, 3.02 mmol) and DBU (0.4 mL) were added in the order given to resin **1** (0.30 g, 0.18 mmol). The resulting mixture was shaken at room temperature for 16 h. After filtration and washing with DMF, a solution of tin(II) chloride dihydrate (2.14 g, 9.47 mmol) in 1-methyl-2-pyrrolidinone (4 mL) was added to the resin and shaking at room

temperature was continued for 9.5 h. Extensive washing with DMF, dichloromethane and methanol, followed by acidolytic cleavage from the support (2 mL dichloromethane, 2 mL trifluoroacetic acid, 0.5 h) and concentration of the liquid phase yielded a solid, which was recrystallized from a mixture of methanol, ethyl acetate and heptane. 31 mg (74%) of indole **3a** was obtained as colorless solid. Mp > 250 °C; LCMS *m/z* 234 (MH^+); IR (KBr) 3448, 2528, 1692 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.57 (s, 3H), 2.74 (s, 3H), 7.79 (d, br, J = 8 Hz, 1H), 8.02 (s, br, 1H), 8.14 (d, J = 8 Hz, 1H), 11.95 (s, br, 0.5H), 12.75 (s, br, 0.5H). (For unknown reasons integrals of acidic protons were lower than calculated). Anal. Calcd. for $C_{12}H_{11}NO_4$ (233.23): C, 61.80; H, 4.75; N, 6.01. Found: C, 61.61; H, 4.75; N, 5.78.

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11. Procedure for the preparation of benzisoxazole **6**: To resin **4** (0.50 g, 0.31 mmol; prepared from Wang resin bound piperazine[1d]) was added as solution of 4-(acetylamino)phenylacetonitrile (1.74 g, 10.0 mmol) in DMF (10 mL), followed by the addition of potassium bis(trimethylsilyl)amide (2.5 mL of a 0.5 mol L^{-1} solution in toluene). The resulting mixture was shaken at room temperature for 18 h, filtered and the resin was washed with 1-methyl-2-pyrrolidinone. A solution of tin(II) chloride dihydrate (2.20 g, 9.75 mmol) in 1-methyl-2-pyrrolidinone (10 mL) was then added and the resulting mixture was shaken at room temperature for 18 h. Extensive washing with DMF, dichloromethane and methanol, followed by acidolytic cleavage from the support (5 mL dichloromethane, 5 mL trifluoroacetic acid, 0.5 h) and concentration of the liquid phase yielded 305 mg of benzisoxazole **6** as a solid, 54%/72% pure by HPLC (214 nm/254 nm). Recrystallization from methanol yielded 103 mg (66%) of **6** as colorless dihydrate. Mp 218–220 °C; LCMS *m/z* 397 (MH^+); ^1H NMR (300 MHz, DMSO-d_6) δ 2.11 (s, 3H), 3.22 (s, br, 4H), 3.50–3.95 (m, 4H), 7.16 (d, br, J = 8 Hz, 1H), 7.79 (s, 1H), 7.88 (d, J = 8 Hz, 2H), 8.10 (d, J = 8 Hz, 2H), 8.21 (d, br, J = 8 Hz, 1H), 9.05 (s, br, 2H), 10.35 (s, 1H). Anal. Calcd for $C_{20}H_{20}N_4O_3 \cdot C_2HF_3O_2 \cdot 2H_2O$ (514.46): C, 51.36; H, 4.90; N, 10.89. Found: C, 51.37; H, 4.81; N, 10.81.