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6-SUBSTITUTED INDOLES FROM o-HALONITROBENZENES

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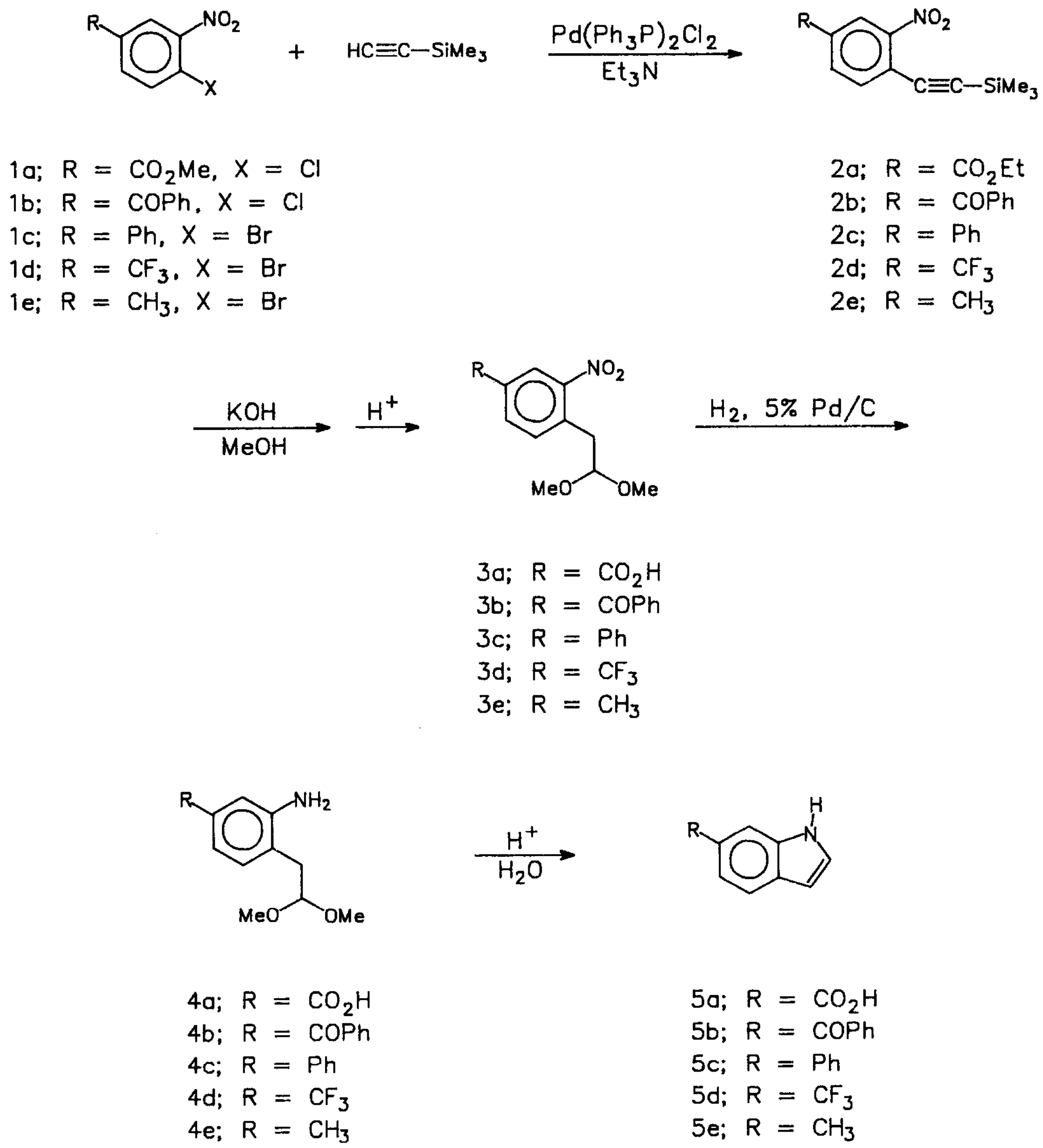
Summary: o-Chloro- and o-bromonitrobenzenes are efficiently converted to 6-substituted indoles in a four step synthesis, proceeding through o-trimethylsilylethynylnitrobenzenes, o-nitrophenylacetaldehyde dimethylacetals and o-aminophenylacetaldehyde dimethylacetals as intermediates.

Indoles containing electron withdrawing groups in the 6-position are historically among the most difficult to obtain. Methods that involve electrophilic ring closures, such as the Fischer or Bischler Syntheses, are generally not applicable to indoles containing only electron-withdrawing groups[1]. We wish to report the development of a novel method for the preparation of such 6-substituted indoles from readily obtainable o-halonitrobenzenes.

The overall reaction scheme is presented in Figure 1. The starting o-halonitobenzenes (1a-e) undergo palladium-catalyzed substitution with ethynyltrimethylsilane to form the o-ethynylnitobenzenes (2a-e). While this reaction type has been described for the substitution of aryl iodine and bromine[2,3], we have found that the presence of an o-nitro group extends the reaction to include the substitution of aryl chlorine as well. In the key step of the synthesis, the trimethylsilylethynes (2a-e) are converted to the dimethylacetals (3a-e) in refluxing methanolic KOH. Under these conditions, the trimethylsilylethynyl group is deprotected followed by base-catalyzed Michael-type addition of methanol to the triple bond yielding the acetals (3a-e). These nitroacetals are catalytically reduced to the corresponding aniline acetals (4a-e), which are in turn cyclized to the indoles (5a-e) in the presence of dilute aqueous acid.

Yields and melting points for all products and intermediates are given in Table 1. The reported yields represent isolated products and are not optimized in most cases. Typical reaction conditions follow.

Figure 1. Synthesis Of 6–Substituted Indoles



1a; R = CO_2Me, X = Cl
1b; R = COPh, X = Cl
1c; R = Ph, X = Br
1d; R = CF_3, X = Br
1e; R = CH_3, X = Br

2a; R = CO_2Et
2b; R = COPh
2c; R = Ph
2d; R = CF_3
2e; R = CH_3

3a; R = CO_2H
3b; R = COPh
3c; R = Ph
3d; R = CF_3
3e; R = CH_3

4a; R = CO_2H
4b; R = COPh
4c; R = Ph
4d; R = CF_3
4e; R = CH_3

5a; R = CO_2H
5b; R = COPh
5c; R = Ph
5d; R = CF_3
5e; R = CH_3

Table 1. Percent Yields, Melting Points(°C)

	2	3	4	5	Overall
a)	86(64–5)	79(124–5)	99(151–3)	97(253–4)[4]	65
b)	75(86–8)	90(69–71)	64(78–80)	89(146–8)	38
c)	96(51–3)	95	99	95(158–61)[5]	86
d)	89(67–9)	87	99	95(107–9)[6]	73
e)	96(55–7)	96	94	78	68

o-Trimethylsilylethynylnitrobenzenes (2a-e)

A nitrogen purged, stirred mixture of the o-halonitrobenzene (0.010 moles), bis(triphenylphosphine)palladium(II) chloride (Aldrich; 0.10 g) and ethynyltrimethylsilane (Silar; 0.018 moles) in triethylamine (Fluka; 25 ml) is heated to 75°C until the halonitrobenzene is consumed (tlc; 15% ether in hexane; 1-4 hrs.). After cooling, the triethylamine hydrohalide is filtered, washed with additional triethylamine, and the combined filtrates evaporated under vacuum. The product is purified by flash chromatography in an appropriate mixture of ether and hexane.

o-Nitrophenylacetaldehyde dimethylacetals (3a-e)

The o-trimethylsilylethynylnitrobenzene (0.010 moles) and KOH (0.050 moles) in methanol (50 ml) is heated at reflux until the reaction is complete (R = carbomethoxy, benzoyl and trifluoromethyl; 20 min.: R = phenyl; 4 hrs.: R = methyl; 11 hrs.). After cooling, acetic acid (0.050 moles) is added and most of the methanol evaporated under vacuum. The product is isolated by diluting with water, extracting into methylene chloride, drying over sodium sulfate and evaporating to dryness under vacuum. The product thus obtained, while generally clean enough for further use, is purified either by recrystallization or by flash chromatography. Under these conditions, the carbomethoxy function of 2a is hydrolyzed[8]. The resulting carboxylic acid 3a is isolated as a precipitate following neutralization of the reaction mixture with dilute aqueous acetic acid.

o-Aminophenylacetaldehyde dimethylacetals (4a-e)

All of the nitro compounds (3a-e) are hydrogenated at 40 lbs. pressure in the presence of 5% Pd/C at room temperature. Except for 3b all the compounds are dissolved in 1% acetic acid in methanol (0.010 moles/100 ml). Better results are obtained for 3b in glacial acetic acid. The lower yield in this case is due to competitive reduction of the benzoyl carbonyl.

6-Substituted indoles (5a-e)

The aminoacetals 4a-d are converted to the corresponding indoles by stirring at 60°C in 1 molar HCl in 50% aqueous ethanol for 30 minutes (0.0080 moles/10 ml). In most cases the indole is obtained as a precipitate from the reaction mixture. Aminoacetal 4e is converted in 50% aqueous acetic acid at 100°C.

The reported examples demonstrate that the 6-substituent can be either electron withdrawing or releasing. However, the first two steps of the synthesis are facilitated when the substituent is electron withdrawing. In cases where both chloro- and bromonitrobenzenes were compared (R = CF_3, CH_3), the Pd-catalyzed substitution of bromide gave higher yields. The use of 2-methyl-3-butyn-2-ol[7] in place of ethynyltrimethylsilane was investigated for R = CO_2Me. Substitution with this alkyne proceeded reasonably well, but deprotection to generate the terminal acetylene did not occur in methanolic KOH. While this study was limited to the synthesis of 6-substituted indoles, there is reason to expect that this synthesis will prove applicable to indoles substituted in all but the 3-position. The generality of the synthesis is currently under investigation.

References and Notes

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