

One-Pot Fischer Indole Synthesis by Zeolite Catalysis

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A one-pot procedure for the synthesis of substituted indoles by heating the parent ketone and a phenylhydrazine in the presence of an acid zeolite catalyst is described. Using 3-hexanone as a unsymmetrical model ketone and a *para*-substituted phenylhydrazine as the co-reagent (H, NO₂, MeO, Cl as substituents) it was found that the ratio of the possible regioisomers of the indoles is highly dependent on the type of zeolite used as the catalyst. Isolated yields of the indoles were in the range 54–98%. It is also shown that zeolites can be used as catalysts in a flow-reactor system to achieve indole synthesis.

The acid catalysed rearrangement/ring closure of arylhydrazones to indoles is known as the Fischer indole reaction. When it is applied to phenylhydrazones derived from unsymmetrical ketones possessing both α and α' methylene groups, two isomeric indoles can be formed. Numerous attempts to control the regiochemistry by selecting certain combinations of solvents and/or acid catalysts, supposed to be selective, have been presented in the literature.¹ In an extensive study on the Lewis acid catalysed reaction² we have shown that the nature of the acid catalyst does not exert any systematic influence at all and that the properties of the solvent have only a weak influence on the regioselectivity of the reaction. The most important factors controlling the regiochemistry are the properties of the starting ketone where the steric bulk of the side-chains is the most important. In a recent paper³ we have shown that the use of zeolites as catalysts for the reaction amplifies the effects of ketone properties and that this offers a means of controlling the regiochemistry. It was found that a one-pot procedure (Scheme 1) could be used for the transformation of the parent ketone and phenylhydrazine into the indoles. It was also found that the distribution of indole isomers was highly dependent on the type of zeolite used, e.g. Morde-nite (H-form) and Zeolite Y afforded totally different results. This was studied with a series of unsymmetrical test ketones selected by their principal properties to assure a sufficient spread in the ketone properties. In this communication we report that the one-pot procedure can be applied to the reaction of substituted phenylhydrazines. One example using a functionalized ketone, methyl 5-oxooctanoate, is also given. To allow a comparison with standard Fischer indolization we also report the results obtained using the corresponding phenylhydrazones as sub-

strates and acetic acid as the catalyst. It is also shown that a selectivity similar to that observed in the batch procedure can be obtained using a flow-reactor in which the ketone and phenylhydrazine are passed through a bed of zeolites.

Methods

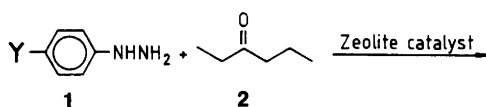
The reactions were monitored by capillary GLC and the isomer distribution was determined from integrated peak areas. It was assumed that isomeric indoles have the same sensitivity in the flame ionization detector.

The identities of the indole isomers were inferred from their mass spectra by analogy to the results reported in Ref. 2. The fragmentation of the indoles is characteristic. The predominant fragmentation is by benzylic cleavage of the alkyl substituents.

Results

One-pot batch procedure. The results obtained with 3-hexanone as the substrate with substituted phenylhydrazines are summarized in Table 1.

With methyl 5-oxooctanoate a substrate, 3-(2-methoxycarbonyl-ethyl)-2-propylindole (**5**) and 3-ethyl-2-(3-methoxycarbonylpropyl)indole (**6**) were formed, see Fig. 1. The following results were obtained: Mordenite afforded



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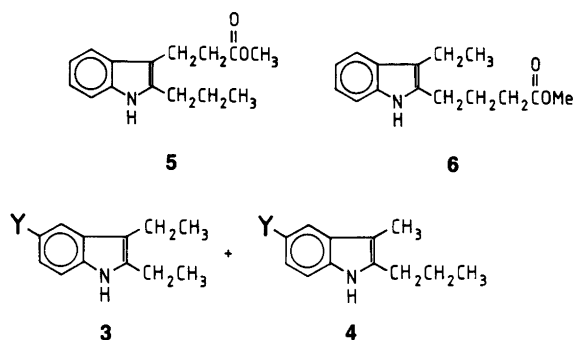


Table 1. Yields and isomer distribution of indoles in the reaction of 3-hexanone with *para*-substituted phenylhydrazines.

<i>para</i> -Substituent	Catalyst ^a	Reaction time/h	Isomer distribution ^b (%)		Yield (%)
			3	4	
H	M	5	10	90	85
	ZY	5	44	56	84
	AA ^c	48	20	80	65
Cl	M	12	19	81	81
	ZY	6	41	59	77
	AA ^c	12	30	70	85
O ₂ N	M	48	13	87	54
	ZY	48	45	55	60
	AA ^c	96	30	70	30
CH ₃ O	M	24	22	78	79
	ZY	24	40	60	98
	AA ^c	24	33	67	99

^aThe following abbreviations are used: M = Mordenite, ZY = Zeolite Y, AA = acetic acid. ^bSee Scheme 1 for identification of indole isomers. ^cThe corresponding phenylhydrazone was heated in acetic acid.

95 % (isolated yield) of a 85/15 mixture of **5/6** after 1 h of reaction. Zeolite Y gave, under the same conditions, 93 % (isolated yield) of a 9/91 mixture of **5/6**. Under standard Fischer conditions in acetic acid, a 65/35 mixture of **5/6** was obtained in 60 % yield.

Flow-through reactor. The following results were obtained when a mixture of 3-hexanone and phenylhydrazine was passed through a bed of zeolite at elevated temperature. Mordenite gave 96 % yield of a 9/92 mixture of **3a/4a** after being passed twice through the column. Zeolite Y afforded, under the same conditions, a 70 % yield of a 45/55 mixture of **3a/4a**.

Experimental

Chemicals. Phenylhydrazine, substituted phenylhydrazines, 3-hexanone, methyl 5-oxooctanoate were commercial *p.a.* or *puriss.* quality chemicals purchased from Aldrich or Janssen and were used as delivered. The zeolites Mordenite (H-form, Si/Al ratio 46.6) and Zeolite Y (Si/Al ratio 34.4) were commercial products from Conteka B.V. (Holland) and were obtained as gifts from EKA Nobel. The zeolites were activated by being heated to 200 °C under reduced pressure (0.1 mmHg) for 5 h. Xylene (isomer mixture) from KEBO was dried over molecular sieves (4 Å).

GLC analyses. These were run on a Carlo-Erba 4160 Fractovap equipped with an FID. A SPB-5 capillary columns (0.3 mm i.d., 25 m) was used. Integrated peak areas were

used for determination of the isomer distribution and a Milton Roy C-10 integrator was used.

GLC-MS analysis. There were performed using an SIL-8 column (0.21 mm i.d., 30 m) coupled to a HP GC/MSD 5830/5970 system. Electron impact (70 eV) was used for ionization.

One-pot batch procedure. The zeolite (1 g) and the ketone (5 mmol) were stirred in 10 ml of xylene at room temperature for 10 min whereafter the phenylhydrazine (**1a-d**) (5 mmol) was added in one portion. The mixture was heated to reflux and maintained at reflux temperature for the time given. After removal of the zeolites by filtration, the solvent was evaporated under reduced pressure. The residue was distilled using a Kugelrohr apparatus and the yields given refer to distilled product mixtures of indole isomers. The boiling points given are the oven temperatures from the Kugelrohr distillation. The nitroindoles obtained from 4-nitrophenylhydrazine decomposed upon attempted distillation and were freed from unchanged starting material by chromatography on silica gel 60 (Merck) using light petroleum-diethyl ether (2:1) as the eluent. The indole isomers could not be separated by this procedure, however.

Standard indolization in acetic acid. The corresponding phenylhydrazone was refluxed in anhydrous acetic acid. Yields refer to isolated products after Kugelrohr distillation. The phenylhydrazone was prepared by azeotropic condensation of the corresponding ketones and phenylhydrazines in benzene. A Dean-Stark trap was used.

Flow-through reactor experiments. The reactor was an electrically heated (Heat-by-the yard^R) glass column, 4 mm i.d., loosely packed with 1.0 g of the zeolite. The column was heated to 150 °C and a solution of 3-hexanone (0.5 g, 5 mmol) and phenylhydrazine (0.54 g, 5 mmol) in 10 ml of xylene was passed through the column with the aid of a syringe. The flow-rate was approximately 1 ml min⁻¹. After being passed once through the column, the eluate was recycled once, and the yields given refer to distilled products after two reaction cycles on the column.

Boiling points and mass spectra of the indoles. The properties of 2,3-diethylindole (**3a**) and 3-methyl-2-propylindole (**4a**) have been given in Refs. 2 and 3. Mass spectra are reported as follows: *m/z* (% relative abundance) [assignment].

5-Chloro-2,3-diethylindole (3b). MS 209 (10.0) [*M*⁺+2], 207 (29.3) [*M*⁺], 194 (30.8) [*M*⁺+2-CH₃], 192 (100.0) [*M*⁺-CH₃, benzylic cleavage of the 3-ethyl substituent], 179 (7.7), 178 (8.4), 177 (19.2), 157 (9.5).

5-Chloro-3-methyl-2-propylindole (4b). MS 209 (10.9) [*M*⁺+2], 207 (26.7) [*M*⁺], 180 (32.4) [*M*⁺+2-Et], 179 (16.0), 178 (100.0) [*M*⁺-Et, benzylic cleavage of the 2-

propyl substituent], 164 (5.8), 143 (28.2), 142 (6.8), 115 (11.5). The boiling point of the **3b/4b** mixture was 190 °C/3 mmHg.

2,3-Diethyl-5-nitroindole (3c). MS 219 (10.0) [$M^+ + 1$], 218 (42.0) [M^+], 203 (100.0) [$M^+ - \text{CH}_3$, benzylic cleavage of the 3-ethyl substituent], 158 (44.6), 115 (18.2).

3-Methyl-5-nitro-2-propylindole (4c). MS 218 (9.4) [M^+], 189 (100.0) [$M^+ - \text{Et}$], benzylic cleavage of the 2-propyl substituent], 143 (40.4), 115 (16.5).

2,3-Diethyl-5-methoxyindole (3d). MS 204 (9.1) [$M^+ + 1$], 203 (37.4) [M^+], 189 (13.5), 188 (100.0) [$M^+ - \text{CH}_3$, benzylic cleavage of the 3-ethyl substituent], 174 (5.8), 173 (18.0), 172 (5.8), 158 (14.1), 130 (7.5).

5-Methoxy-3-methyl-2-propylindole (4d). MS 204 (5.0) [$M^+ + 1$], 203 (32.7) [M^+], 175 (13.8), 174 (100.0) [$M^+ - \text{Et}$, benzylic cleavage of the 2-propyl substituent], 159 (5.3), 142 (6.7), 131 (22.5), 130 (11.3). The boiling point of the **3d/4d** mixture was 185 °C/3 mmHg.

3-(2-Methoxycarbonylethyl)-2-propylindole (5). MS 245 (38.2) [M^+], 172 (100.0) [$M^+ - \text{CH}_2\text{CO}_2\text{CH}_3$, benzylic cleavage of the 3-propionic ester substituent], 157 (18.5), 144 (22.7), 143 (18.9).

3-Ethyl-2-(3-methoxycarbonylpropyl)indole (6). MS 245 (98.6) [M^+], 230 (87.0) [$M^+ - \text{CH}_3$, benzylic cleavage of the 3-ethyl substituent], 170 (81.9), 158 (100.0) [McLafferty fragmentation of the 2-butyric ester substituent], 144 (41.3), 143 (69.8). The boiling point of the **5/6** mixture was 140 °C/3 mmHg. The product mixture decomposed on standing in room temperature.

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