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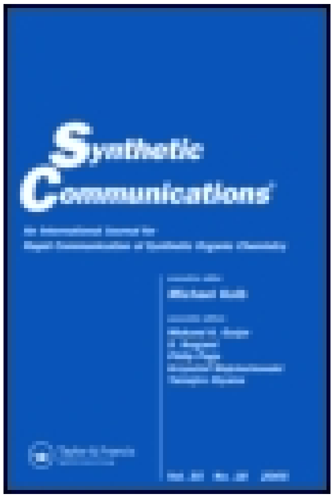

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A Convenient Modification of the Fischer Indole Synthesis with a Solid Acid

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A convenient modification of the Fischer indole synthesis with a solid acid

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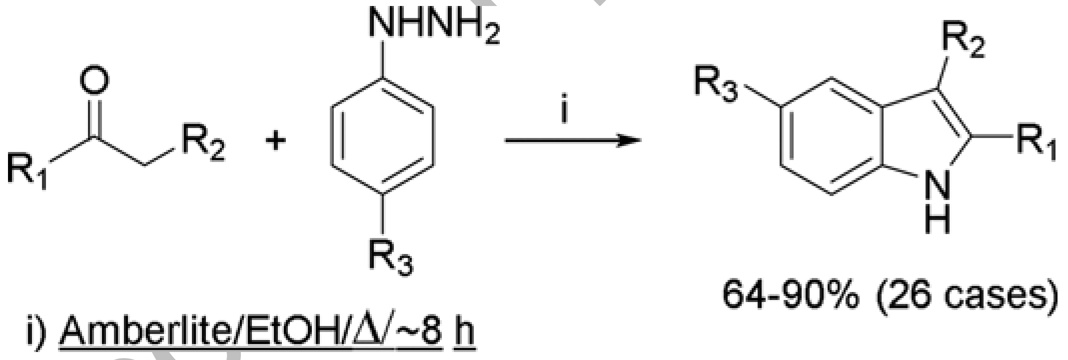
Abstract

A new one-pot version of the titled reaction involves heating a mixture of a carbonyl compound, a phenylhydrazine and the cation exchange resin Amberlite® IR 120 in refluxing ethanol. A variety of enolizable aldehydes and ketones, and several substituted phenylhydrazines could thus be converted to the corresponding indoles in excellent yields (70-88%). Reaction times were typically 6-10 h, the resin being then filtered off and the product isolated after minimal work-up.



INTRODUCTION

The indole skeleton is famously present in a very large number of biologically-active molecules, both naturally-occurring and synthetically-engineered.[1-3] The essential amino acid tryptophan and an eponymous group of alkaloids come easily to mind,[4] but there also exists an expanding clutch of synthetic species covered by trade names that attest to their commercial value. The skeleton has thus been the target of several synthetic strategies and approaches spread over the preceding century. The vast majority of these start from an aromatic precursor and fashion the fused pyrrole moiety by various tactics, whether ingenious or deliberate.

One such, the Fischer synthesis, is a classical reaction that hails from the formative era of modern organic chemistry,[1–3] but continues to be pursued for both its synthetic value and mechanistic fascination.[5,6] (The key C-C bond forming step involves a symmetry-allowed [3,3]-sigmatropic shift, *vide infra.*) Originally, the reaction was effected starting from phenylhydrazones (**1,** Scheme 1), simple precursors that are indeed readily prepared. Heating these in an appropriate solvent (*e.g.* EtOH) along with an acid catalyst leads to the formation of the corresponding indoles (**4**).

The transformation is believed to occur *via* the initial isomerization of **1** to the ene-hydrazine **2,** which requires the presence of an α proton in the hydrazone moiety. The **2** then undergoes a [3,3]-sigmatropic rearrangement to form the di-imine **3,** which re-aromatizes and undergoes internal nucleophilic attack, to lead finally to the indole **4**.

The acid catalyst is believed to facilitate the isomerisation of **1** to **2,** a variety of Brønsted and Lewis acids having been employed to effect the transformation. Interestingly, $ZnCl_2$, one of the earliest catalysts thus employed, often continues to be the catalyst of choice. A problem with the reaction, however, is that the ammonia by-product neutralizes the acid catalyst, which thus must be employed at stoichiometric levels.

An interesting variant of the Fischer indole synthesis involves the *in situ* formation of the phenylhydrazone from a carbonyl precursor and phenylhydrazine. This ‘one-pot’ reaction is feasible because hydrazone formation is also promoted by acid; and the reaction can be run without removal of the water by-produced with the intermediate hydrazone, as the aromatic stability of the final indole product shifts this initial equilibrium.

The increasing importance of environmentally-friendly ‘green’ methodologies has led to the use of aqueous media, or even solvent-free conditions, for effecting the Fischer indole synthesis.[7,8] The catalysts employed, however, are not always easily obtained; in fact, the solvent-free versions often employ the acid catalyst in excess, possibly to overcome poor diffusion of the reactants in the semi-solid or viscous reaction medium.

It was thus of interest to explore alternative acid catalysts that are both readily available and easily recovered from the reaction medium upon work-up. This led to the possibility of using resin-based acids, the results of our studies being described in detail below. Interestingly, although such polymer-bound cation exchangers have been known for long, they have not been employed extensively in the Fischer indole synthesis.[7]

RESULTS AND DISCUSSION

In exploratory studies, a mixture of phenylhydrazine, a ketone (typically, cyclohexanone) and a cation exchange resin (*e.g.* Dowex® or Amberlite®) was refluxed in a solvent (MeOH, EtOH, MeCN, $CHCl_3$, EtOAc and dioxane) over several hours. The reaction was monitored by thin layer chromatography, which also indicated the formation of the expected indole product. Reaction conditions were then optimized in terms of catalyst, solvent and the time taken for completion of the reaction. The optimized conditions and yields are shown in Table 1 (full characterization data can be found in the supplementary information file).

The reaction has been performed herein with a variety of ketones (**5,** Scheme 2) and several *para* substituted phenylhydrazines (**6**), the final indole product (**8**) being isolated in generally excellent yields in a reasonable period of time (typically ~ 80% in 6-10 h). Interestingly, cyclic ketones (items 8-17) generally took longer for completion of reaction, as did certain aromatic ketones (items 19-26). The cyclic ketones are possibly sterically hindered, with the derived indole products also possibly strained because of the ring fusion; the aromatic ketones would be unreactive because of conjugation between the carbonyl and aromatic moieties. Also, in the case of ketones with two different α-acidic sites, the indole regio-isomer derived from the more stable ene-hydrazine (**I**) was apparently formed.

The effect of the *para* substituent (R_3) in the phenylhydrazone on the reaction time was unpredictable. However, the time taken was apparently enhanced in many cases, regardless of the nature of R_3. This may be due to competing kinetic and thermodynamic factors, electron- donating R_3 enhancing the nucleophilicity of **6,** but electron-withdrawing R_3 possibly stabilizing **8** (and *vice-versa*). (These conclusions are clearly tentative, but they are apparently similar to previous observations.[9,10] Also, attempts to recycle the catalyst led to considerably lower yields, so were not pursued further in view of its ready availability and minimal requirements at laboratory scales.)

The replacement of the normally employed soluble acid catalysts by a solid acid herein is a significant improvement, as the catalyst is generally employed at stoichiometric levels (often in large excess) in the Fischer indole synthesis.[11] This is because of the liberation of ammonia as a by-product, which neutralizes a large part of the acid catalyst. The advantages of a solid acid catalyst are clearly greater on larger scales, thus leading to environmentally sustainable ('green') processes.

CONCLUSIONS

A convenient modification of the conventional Fischer indole synthesis has been developed, essentially characterized by simplicity of operation and work-up. These derive from the fact that the normally employed soluble acid catalyst has been replaced by a solid acid (the Amberlite® cation exchange resin). Excellent yields have been realized with a wide range of reactants, with reasonable reaction times. Additional benefits, particularly on large scales, involve environmental concerns, as the acid catalyst is normally employed in excess in the Fischer indole synthesis.

SUPPORTING INFORMATION

Supporting Information: Full characterization data for all compounds reported herein. This material can be found via the ''Supplementary Content'' section of this article's webpage.

EXPERIMENTAL

Typical Procedure

A mixture of the carbonyl compound (**5,** 1.0 mmol), arylhydrazine (**6,** 1.2 mmol) and the solid acid (**7,** Amberlite®, 1.5 g, obtained from Aldrich Chemical Co.) was refluxed in absolute ethanol (10 ml) for 8 h. The reaction was monitored by tlc, and upon completion the mixture was cooled to room temperature, the catalyst filtered off and washed thoroughly with ethyl acetate (30 ml). The combined organics were washed with water, dried (Na_2SO_4) and concentrated *in vacuo.* The resulting residue was chromatographed on a silica gel column eluting with ethyl acetate-hexane mixtures, to obtain the purified indole (**8**). This was fully characterized by IR, 400 MHz ^{1}H NMR and HRMS, and melting point (solids).

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REFERENCES

[1] Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry;* Katritzky, A. R.; Rees, C. W.; Bird, C. W.; Cheeseman, G. W. H., (Eds.); Pergamon: Oxford, 1984; Vol. 4, pp. 313-376.

[2] Joule, J. A.; Mills, K. *Heterocyclic Chemistry* 4th ed.; Blackwell Science Ltd.: Oxford, 2000; pp. 353-370.

[3] Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure,* 6th ed.; John Wiley: Hoboken, 2007; pp. 1674-1676.

[4] Barbour, P. M.; Marholz, L. J.; Chang, L.; Xu, W.; Wang, X. *Chem. Lett*. **2014**, *43*, 572–578. doi:10.1246/cl.131230.

[5] Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321–1325. doi: 10.1002/ejoc.200900077.

[6] Kapoor, K. K.; Ganai, B. A.; Kumar, S.; Andotra, C. S. *Synth. Commun.* **2006**, *36*, 2727–2735. doi: 10.1080/00397910600764766.

[7] Xu, D-Q.; Wu, J.; Luo, S-P.; Zhang, J-X.; Wu, J-Y.; Du, X-H.; Xu, Z-Y.; *Green Chem.*, **2009**, *11*, 1239–1246. doi: 10.1039/b901010f.

[8] Matsumoto, K.; Tanaka, A.; Yukio, I.; Hayashi, N.; Toda, M.; Bulman, R. A. *Heterocycl. Commun.* **2003**, *9*, 9-12. doi: 10.1515/HC.2003.9.1.9.

[9] Ishii, H. *Acc. Chem. Res.* **1981**, *14*, 275-283.

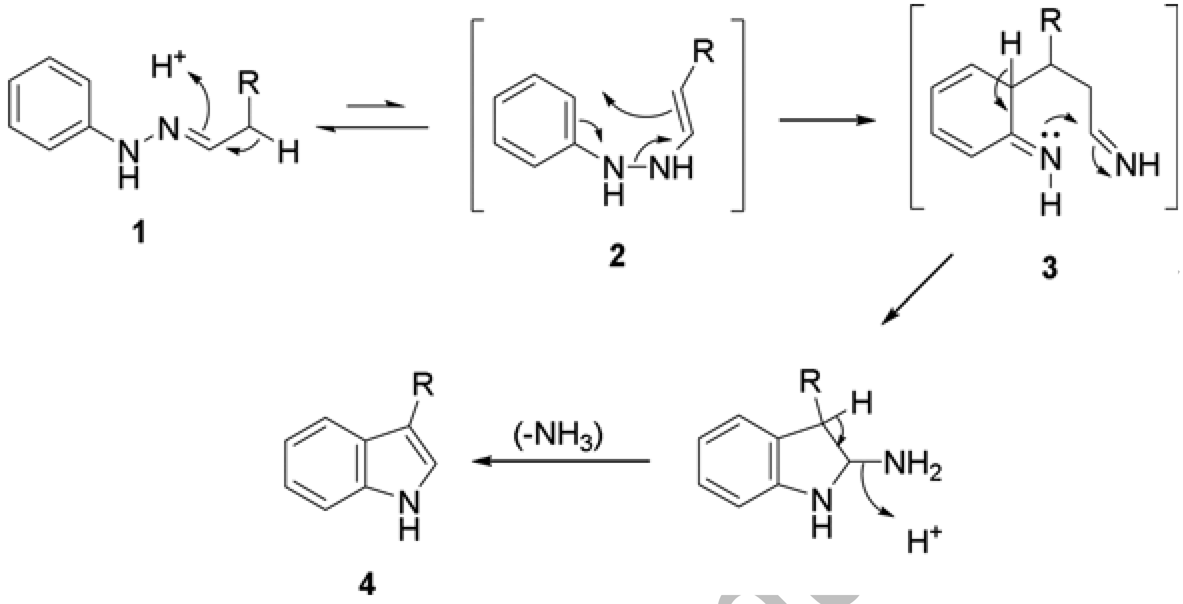
[10] Robinson, B. *Chem. Rev.* **1969**, *69*, 227-250.

[11] Ishii, H.; Murakami, Y.; Furuse, T.; Hosoya, K.; Ikeda, N. *Chem. Pharm Bull.* **1973**, *21*, 1495-1505.

Table 1. Conditions and yields (of **8**) for the Fischer indole synthesis in Scheme 2

Item	R_1	R_2	R_3	Time (h)	Yield (%)
1	Me	Me	H	8	80
2	Et	Me	H	8	75
3	Me	Et	MeO	10	75
4	H	Me_2CH	H	8	70
5	Me	Me_2CH	H	10	82
6	H	*n*-C_5H_{11}	H	6	72
7	Me	*n*-C_5H_{11}	MeO	10	84
8	Cyclopentanone		H	10	84
9	Cyclohexanone		H	12	85
10	Cyclohexanone		MeO	10	85
11	Cyclohexanone		CN	14	80
12	Cyclohexanone		Br	12	88
13	4-Methylcyclohexanone		H	10	82
14	4-*t*-Butylcyclohexanone		MeO	8	90
15	Cycloheptanone		Br	10	88
16	Cyclooctanone		H	12	80
17	Cyclododecanone		H	12	78
18	Me	$PhCH_2$	MeO	7	85
19	Ph	Me	MeO	6	88
20	*p*-Cl-C_6H_4-	Me	Br	10	82
21	Ph	Ph	H	12	74
22	$PhCH_2$	Ph	H	12	80
23	*p*-(MeO)-C_6H_4-	*p*-(NO_2)-C_6H_4-	H	14	72
24	*p*-(NO_2)-C_6H_4-CH_2	*p*-(NO_2)-C_6H_4-	H	10	64
25	*β*-Tetralone		H	10	86
26	*β*-Tetralone		MeO	7	90

Scheme 1. The Fischer indole synthesis with the accepted mechanism



Scheme 2. The one-pot Fischer indole synthesis starting from a carbonyl compound (**5**) and a phenylhydrazine (**6**) catalyzed by Amberlite® IR 120 (**7**) to yield the indole **8;** the pattern of substitution observed in **8** implies that the reaction occurs via the ene-hydrazine **I**