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Fischer indolisation of 2,6-dialkyl and 2,4,6-trialkylphenylhydrazones of diketones and ketoesters☆

Shambabu J. Maddirala,† Vidya S. Gokak,‡ Sharanabasava B. Rajur§ and Linganagouda D. Basanagoudar*

Department of Chemistry, Karnatak University, Dharwad 580 003, India

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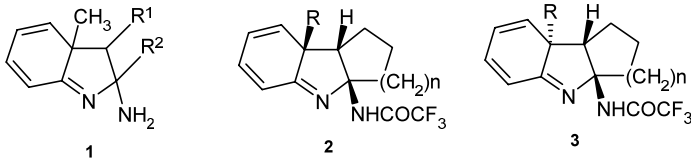
Abstract—Unlike the migration of a methyl group observed in the $ZnCl_2$ or acetic acid-catalysed indolisation of phenylhydrazones, dry ethanolic HCl catalysed indolisation of 2,6-dimethyl- and 2,4,6-trimethylphenylhydrazones of various substituted butane-2,3-diones and ethyl pyruvates yields 7-methyl- and 5,7-dimethyl-3-substituted indoles indicating elimination of an *ortho*-methyl group during indolisation.

The Fischer indole synthesis, which is based on the discovery[1] that cyclisations of arylhydrazones form indoles, has become one of the most versatile and widely studied reactions in organic chemistry as it provides a versatile and convergent route to a wide variety of indole derivatives. Owing to its numerous synthetic applications, the mechanism of the reaction has attracted much attention. A number of reaction pathways have been proposed for the indolisation reaction, but the mechanism proposed by Robinson and Robinson[2a] in its reformulated form by Carlin and Fischer[2c] is the most widely accepted and is well supported by polarisation studies,[3] labelling experiments[4] and isolation of reaction intermediates. Dienylimines of the kind **1**,[5a] **2**,[5b] and **3**[5b] have been isolated and characterised providing good evidence for the postulated reaction mechanism, including stereochemical rationalisation.

One of the strongest supports for Robinson's mechanism is from the studies of group migration during the reaction, particularly of halogens[6] and alkyl groups.[7a,b] In addition to group migration, some anomalous reactions[7d,e] such as elimination and substitution reactions have also been observed lending support to the proposed mechanism. It has been ascertained that the mechanistic details of the reaction depend upon the reaction conditions, nature of hydrazone substrate, nature of cyclising agent and the nature of the solvent. So, it is doubtful if any definitive mechanism applies under all conditions.

2,6-Dialkyl substituted phenyl hydrazones have been important intermediates in mechanistic studies of Fischer indolisation reactions.[7] Indole derivatives are known to be formed by migration of an alkyl group (usually a methyl group) to the adjacent C-atom (i.e. a 1,2-shift)[7a,b] or to the C-atom in the *para* position (a 1,4-shift).[7c] In some cases a methyl group was observed to be lost but its fate was not established.[8]

During the course of our studies[9] on the synthesis of indole-fused heterocycles, a number of 3-substituted



1 2 3

Keywords: indole; phenylhydrazones; Fischer indolisation; Japp–Klingemann procedure.
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* Corresponding author.
† Present address: Ciba India Private Limited, Goregaon, Mumbai 400 063, India.
‡ Present address: Pearl Organics Limited, Patalganga Industrial Area, Mumbai 410207, India
§ Present address: CreaGen Biosciences, Inc. Needham, MA, USA

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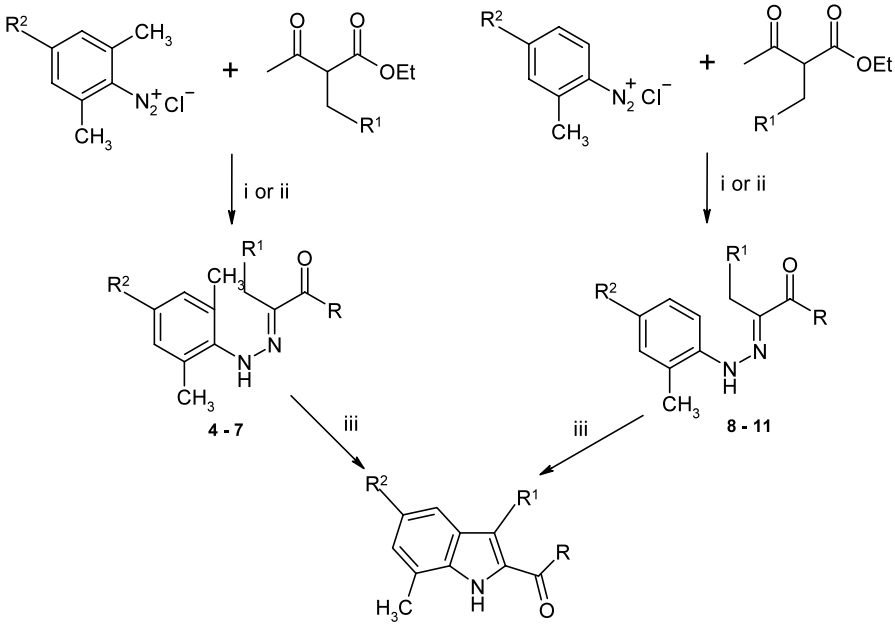
2-acetylindoles and substituted ethyl indole-2-carboxylates were synthesised via Fischer indolisation of appropriate *N*-unsubstituted phenyl hydrazones using HCl as the cyclising agent. Although, Fischer indolisation of 2,6-dimethylphenylhydrazones of ethyl pyruvates has been studied, 2,6-dimethylphenylhydrazones of diketones that would yield 2-acetylindoles on Fischer indolisation have not been explored. It was, therefore, decided to undertake Fischer indolisation of such *ortho* disubstituted phenylhydrazones, namely, 2,6-dimethylphenylhydrazones of various substituted butane-2,3-diones **4**–**7** with the purpose of checking the course of indolisation and the effect of the nature of the substituents of these diones on the reaction course. The hydrazones were obtained by the modified Japp–Klingemann procedure.[10a] Fischer indolisation of these hydrazones **4a**–**7a**, using ethanolic hydrogen chloride,[10b] furnished products, in 15–35% yields, whose analytical data and in particular NMR spectral data indicated the presence of only one (instead of two) aromatic methyl groups, suggesting the loss of one of the *ortho*-methyl groups during cyclisation. This fact was confirmed by the independent synthesis of these indoles **12**–**15**, in 32–62% yields, from the appropriate hydrazones **8a**–**11a** under identical conditions. The elemental analyses, IR and ^{1}H NMR spectra of indoles **12**–**15** obtained from hydrazones **4a**–**7a** agreed well with those obtained from hydrazones **8a**–**11a** confirming the elimination of the *ortho*-methyl groups. Further, when 2,4,6-trimethyl analogues of the above phenylhydrazones **4b**–**7b** were subjected to similar indolisation, the same type of products, with methyl groups having been lost, were obtained and were again confirmed by independent syntheses of the indoles from hydrazones **8b**–**11b** as depicted in Scheme 1.

To verify the generality of this loss of methyl groups during cyclisation, we subjected 2,6-dimethylphenylhydrazones of ethyl pyruvates **4c**–**7c** and the 2,4,6-trimethyl analogues of ethyl 2-ketobutyrates **4d**–**7d**, prepared using the Japp–Klingemann procedure, to Fischer indolisation. Ethyl indole-2-carboxylates **12c**–**15c**, **12d**–**15d** in 12–40% yields, respectively, were the products of these reactions as concluded from ^{1}H NMR spectral and analytical data. The structures of the ethyl indole-2-carboxylates **12c**–**15c** and **12d**–**15d** were confirmed by independent syntheses from appropriate hydrazones **8c**–**11c** and **8d**–**11d** in 22–87% yields.

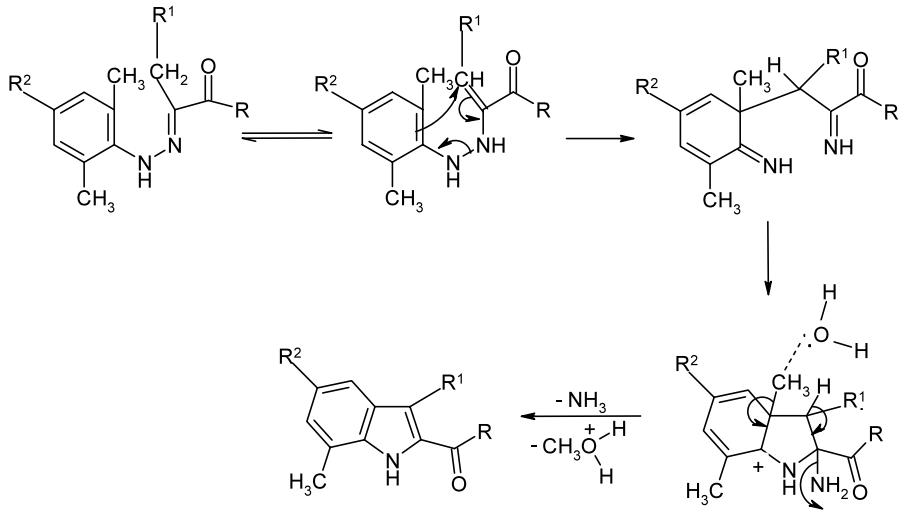
We could not trace the fate of the eliminated methyl groups but the formation of products forces us to accept the view proposed by Bajwa and Brown[8] that the *ortho*-methyl group is eliminated as a methyl carbocation whose mechanism may be depicted as shown in Scheme 2. The cyclisation and subsequent amortisation of the dienone-imine intermediate appears to be the main driving force for the elimination of the methyl



Entry Nos	R^1
4, 8, 12	H
5, 9, 13	CH_3
6, 10, 14	C_6H_5
7, 11, 15	$CH_2C_6H_5$

Entry Nos.	R	R^2
a	CH_3	H
b	CH_3	CH_3
c	OC_2H_5	H
d	OC_2H_5	CH_3

Scheme 1. *Reagents*: (i) NaOH–ethanol/AcONa; (ii) KOH–ethanol; (iii) ethanolic dry HCl.



Scheme 2. Mechanism for the elimination of the methyl group.

group as a carbocation, probably, coordinated with a good nucleophile (H_2O) via a concerted path. It appears that the nature of the ketone or pyruvate has no influence on the course of indolisation.

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10. (a) **General procedure**: The phenylhydrazones **4**–**11a**,**b** were prepared in 62–88% yields by a modified Japp–Klingemann procedure, while the hydrazones **4**–**11c**,**d** were obtained by the usual Japp–Klingemann procedure in 60–90% yields. Hydrazones **4a**, **6a**–**8a**, **10a**, **11a**, **6b**, **7b**, **8b**, **10b**, **11b** and **8d** were solids and all other hydrazones were viscous oils.
(b) **General procedure for cyclisation of phenylhydrazones**: Dry hydrogen chloride gas was passed into a solution of appropriate phenylhydrazone in ethanol until saturated. The solution was then heated under reflux on a steam bath for 3 h, then cooled and poured onto crushed ice. The whole solution was extracted with ether. The ether solution was washed with water, dried over anhydrous Na_2SO_4 and the ether was removed by distillation under reduced pressure. The residual solid was purified by column chromatography over alumina using benzene as eluant. (c) With phenylhydrazones **4a** and **8a** cyclisation could not be effected. Attempted cyclisation did not give the expected product, but the starting phenylhydrazone was recovered (100%).
Spectroscopic data for selected compounds (analytical and spectroscopic data for all the compounds associated with this article can be found on-line.):
Compound **13a** from **5a** Yield 23% (35% from **9a**), melting point 158°C; IR (cm^{-1}) 3352, 1635; ^1H NMR ($CDCl_3$) 200 MHz: δ 2.47 (s, 3H), 2.64 (s, 6H), 7.05 (t, $J=7.9$ Hz, 1H), 7.13 (d, $J=7.0$ Hz, 1H), 7.53 (d, $J=7.9$ Hz, 1H), 8.85 (brs, 1H). Anal. calcd for $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.49. Found: C, 77.52, H, 7.02, N, 7.71%. Compound **13b** from **5b** Yield 21% (32% from **9b**), melting point 198°C; IR (cm^{-1}) 3342, 1645; ^1H NMR ($CDCl_3$) 200 MHz: δ 1.88 (s, 3H), 2.12 (s, 3H), 2.23 (s, 3H), 2.35 (s, 3H), 7.1–7.2 (m, 2H), 9.0 (brs, 1H). Anal. calcd for $C_{13}H_{15}NO$: C, 77.61; H, 7.46; N, 6.96. Found: C, 77.81, H, 7.76; N, 7.19%. Compound **13c** from **5c** Yield 28% (48% from **9c**), melting point 148°C; IR (cm^{-1}) 3335,

1688; ^{1}H NMR ($CDCl_3$) 200 MHz: δ 1.44 (t, $J=7.1$ Hz, 3H), 2.49 (s, 3H), 2.60 (s, 3H), 4.42 (q, $J=7.1$ Hz, 2H), 7.06 (t, $J=7.7$ Hz, 1H), 7.11 (d, $J=7.0$ Hz, 1H), 7.50 (d, $J=7.6$ Hz, 1H), 8.58 (brs, 1H). Anal. calcd for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91, N, 6.45. Found: C, 72.06, H, 7.04, N, 6.58%. Compound **13d** from **5d** Yield 22% (62% from **9d**), melting point 153°C; IR (cm^{-1}) 3450, 1705; ^{1}H NMR ($CDCl_3$) 200 MHz: δ 1.44 (t, $J=7.1$ Hz, 3H), 2.43 (s, 3H), 2.46 (s, 3H), 2.57 (s, 3H), 4.42 (q, $J=7.1$ Hz, 2H), 6.96–7.28 (2s, 2H), 8.51 (brs, 1H). Anal. calcd for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.36, N, 6.06. Found: C, 72.91, H, 7.65, N, 6.16%.