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A direct and simple approach for the synthesis of indole-3-propanol and its acetates from dihydropyran

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Abstract A general method was developed for the one-pot synthesis of highly functionalized indoles from simple, commercially available phenylhydrazine hydrochlorides and dihydropyran. Synthesis of indole-3-propanol and its acetates was studied extensively for appropriate acetic acid and water mixture as the solvent.

Keywords Indole-3-propanol; Indole-3-propyl acetate; Acetic acid; Phenylhydrazine hydrochloride; Dihydropyran.

Introduction

There is a considerable interest in efficient methods to prepare indole derivatives, due to the methodological challenges involved and the presence of these heterocycles at the core of many bioactive structures, both natural and synthetic [1]. Tryptophol homologs represent an important class of powerful intermediates in organic synthesis. The important structurally diverse pharmaceutical agents, which are derived from tryptophol homologs include commercial drugs: sumitriptan, indomethacin, tryptophanes, *etc*. Indole-3-alkyl alcohols are fundamental building blocks in organic synthesis and their preparation is an important industrial goal. Among the diverse and creative approaches that have been discovered [2], the *Fischer* indole reaction remains the bench-mark to which other methods are compared [3]. Since its discovery in the 1880s by *Emil Fischer*, various catalysts have been used to effect the cyclization of aryl hydrazones derived from ketones. Alternative catalysts, including *Brønsted* acids (H_2SO_4, HCl, *PPA*, *Ac*OH) [4], *Lewis* acids ($ZnCl_2$, $TiCl_4$, PCl_3) [5], and solid acids (zeolite, montmorillonite clay) [6], have been reported for the synthesis of the indole nucleus. These conditions however often suffer from low yields and involve two step processes (*i.e.* hydrazone formation and [3 + 3] rearrangement) [7]. Although acetic acid has not been employed for the synthesis of indole-3-alkyl alcohols, but very recently *Kevin et al*. [8] has attempted the synthesis of tryptophols in 4% aqueous H_2SO_4 and obtained tryptophols in 50% yield and the remaining 50% was the result of formation of triol. To avoid the formation of the latter they used acetonitrile as co-solvent. However, the use of sulfuric acid is still a disadvantage due to its corrosive nature and additional usage of co solvent is also required.

Hence, in continued substantial interest to develop methods requiring mild reaction conditions, herein we wish to report a convenient and efficient synthesis one-pot synthesis of indole-3-propanol and its acetates by the reaction of phenylhydrazine hydrochloride with cyclic enol ethers in presence of

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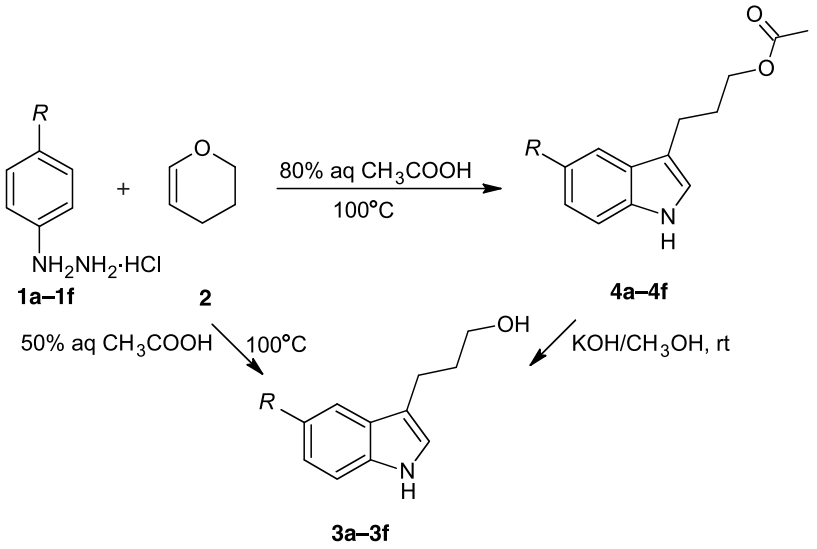


Scheme 1

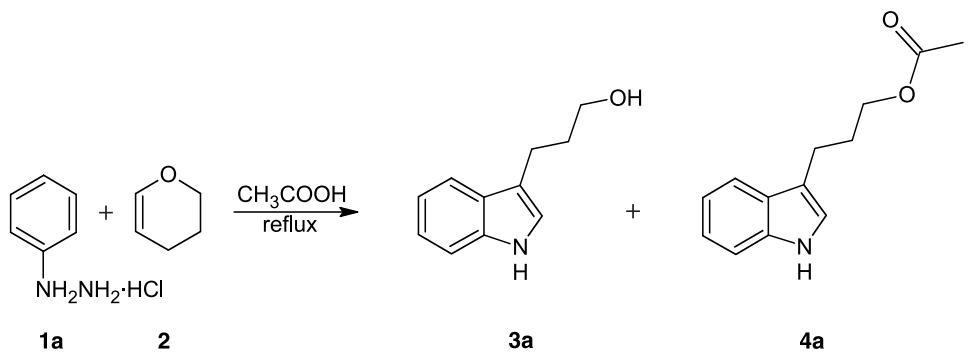
glacial acetic acid as medium and catalyst as well. Acetic acid promoted synthesis of 3-substituted indoles from phenylhydrazine hydrochloride and cyclic enol ethers has thus proven to be a highly attractive and powerful alternative.

Results and discussions

When dihydropyran (**2**) was added to a solution of phenylhydrazine hydrochloride (**1a**) in acetic acid at reflux temperature (Scheme 2), indole **3a** was obtained in 4% isolated yield. The major product of the reaction was the ester **4a**, resulting from further reaction of **3a** with acetic acid and formation of side products were observed. After considerable study on the formation of **4a**, it was observed that in 80% aqueous acetic acid at 100°C, the formation of side product was reduced considerably and the isolated yield of **4a** was increased significantly (75%).

By adopting the optimized condition and in order to widen the scope of this approach towards the synthesis of indole-3-alkyl acetate we explored the one-pot reaction between a wide variety of functionalized phenylhydrazine hydrochlorides with dihydropyran by using 80% aqueous acetic acid. The results are shown in the Table 1.

Since our initial aim was to obtain indole-3-alkyl alcohol, we altered the reaction conditions. During our study, we suspected that **4a**–**4f** were produced due to the high concentration of acetic acid in the reaction. Hence to avoid the formation of acetates, we thought of increasing the concentration of water in the reaction medium. It was observed that addition of water to the reaction significantly improved the reaction profile, producing less than 3% of **4a**. In 50% aqueous acetic acid, the reaction proceeded smoothly to afford the indole-3-propanol **3a** in 92% yield. Furthermore the reaction was carried out in



Scheme 2

Table 1 Synthesis of indole-3-propyl acetate

Products	*R*	Time/min	Yields/%[a]
3a	H	140	75
3b	*Me*	120	70
3c	O*Me*	120	68
3d	F	170	70
3e	Cl	180	65
3f	Br	150	55

[a] isolated yields

Table 2 Synthesis of indole-3-propanol

Products	*R*	Time/min	Yields/%[a]
4a	H	55	92
4b	*Me*	45	96
4c	O*Me*	50	92
4d	F	70	88
4e	Cl	75	84
4f	Br	75	84

[a] isolated yields

water to know the effect of acetic acid in the reaction, but only formation of aryl hydrazones was observed. The results obtained with other substituents are given in Table 2. Alternatively, indole-3-propanols were also obtained from the corresponding acetates on treatment with KOH in ethanol at room temperature.

In conclusion, we demonstrated that phenylhydrazine hydrochloride and dihydropyran can be transformed into functionally diversified indole-3-propanols and acetates in a direct and simple procedure. The resulting products are of considerable interest as building blocks, since their functional group should allow a variety of subsequent synthesis modifications.

Experimental

All the melting points were recorded in open capillaries. The purity of the compounds was checked by TLC on silica gel and they were purified by column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-400 MHz spectrometer using *TMS* as an internal standard. IR spectra were obtained using a FTS-135 spectrometer instrument. Mass spectra were recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer. Elemental analyses (C, H, N, O) were conducted using the Elementar Vario EL III; their results were in favorable agreement with the calculated values. The compounds **3a**–**3f**, are known and their identities were proven by means of IR, NMR, and mass spectra. Herein we describe spectral data for **4a**–**4f**, which could not be found in literature.

*General procedure for the Fischer indole reaction for the synthesis of **3***

To a solution of 0.144 g phenylhydrazine · HCl (1.0 mmol) in 2 cm^3 50% aqueous acetic acid was added 0.084 g dihydropyran (1.0 mmol) drop-wise over 2 min at room temperature. The reaction was stirred at 50°C for 10 min and refluxed for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with 20 cm^3 saturated aqueous $NaHCO_3$ solution and extracted with 2×15 cm^3 ethyl acetate. The combined organic layers were dried ($NaSO_4$), concentrated, and the crude product was purified by column chromatography on silica gel (60–120 mesh, ethyl acetate:petroleum ether, 3:7).

*General procedure for the Fischer indole reaction for the synthesis of **4***

To a solution of 0.144 g phenylhydrazine · HCl (1.0 mmol) in 80% aqueous acetic acid was added 0.092 g dihydropyran (1.1 mmol) drop-wise over 2 min at room temperature. The reaction was refluxed for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with 20 cm^3 saturated aqueous $NaHCO_3$ solution and extracted with 2×15 cm^3 ethyl acetate. The combined organic layers were dried ($NaSO_4$), concentrated and the crude product was purified by column chromatography on silica gel (60–120 mesh, ethyl acetate:petroleum ether, 3:7).

3-(1H-Indol-3-yl)propyl acetate (**4a**, $C_{13}H_{15}NO_2$)
Pale yellow viscous oil; IR (KBr): $\bar{\nu} = 3522$, 3401, 1742, 1426, 1241 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.01$ (br s, 1H), 7.59 (dt, 1H, $J = 7.8$, 1.1 Hz), 7.32 (dt, 1H, $J = 8.0$, 0.8 Hz), 7.19 (ddd, 1H, $J = 8.0$, 7.1, 1.3 Hz), 7.13 (dd, 1H, $J = 8.2$, 1.2 Hz), 7.01(d, 1H, $J = 0.9$ Hz), 4.15 (t, 2H, $J = 6.3$ Hz), 2.85 (dt, 2H, $J = 7.6$, 0.8 Hz), 2.08 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.3$, 136.5, 127.1, 121.5, 121.1, 119.0, 118.8, 115.8, 109.5, 62.9, 32.9, 21.5, 17.3 ppm; MS: $m/z = 218$ (M + 1).

3-(5-Methyl-1H-indol-3-yl)propyl acetate (**4b**, $C_{14}H_{17}NO_2$)
Pale yellow viscous oil; IR (KBr): $\bar{\nu} = 3458$, 3428, 1748, 1451, 1245, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$ (br s, 1H), 7.44 (s, 1H), 7.28 (d, 1H, $J = 8.2$ Hz), 7.10 (dd, 1H, $J = 8.3$, 1.1 Hz), 6.88 (d, 1H, $J = 0.98$ Hz), 4.13 (t, 2H, $J = 6.3$ Hz), 2.80 (dt, 2H, $J = 7.5$, 0.9 Hz), 2.53 (s, 3H), 2.08 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 171.2, 136.4, 127.3, 122.9, 121.2, 120.3, 119.1, 117.1, 116.6, 62.9, 33.3, 21.2, 17.5, 16.6 ppm; MS: $m/z = 231$ (M+).

3-(5-Methoxy-1H-indol-3-yl)propyl acetate (**4c**, $C_{14}H_{17}NO_3$)
Pale yellow viscous oil; IR (KBr): $\bar{\nu} = 3358$, 3257, 1748, 1678, 1499, 1245, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$ (br s, 1H), 7.28 (d, $J = 8.6$, 1H), 7.13 (m, 2H), 6.88 (t, 1H, $J = 7.4$ Hz), 4.01 (t, 2H, $J = 6.5$ Hz), 3.78 (s, 3H), 2.81 (dt, 2H, $J = 6.9$, 0.7 Hz), 2.10 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.1$, 152.8, 132.0, 127.9, 122.4, 120.5, 117.1,

115.9, 112.6, 103, 62.9, 33.5, 22.1, 17.2 ppm; MS: $m/z = 247$ (M+).

3-(5-Fluoro-1H-indol-3-yl)propyl acetate (**4d**, $C_{13}H_{14}FNO_2$) Pale yellow semi solid; IR (KBr): $\bar{\nu} = 3423, 2956, 1581, 1449, 1370, 1241, 1048\,cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.18 (br s, 1H), 7.24 (dd, 1H, $J = 7.4$, 2.2 Hz), 7.21 (m, 1H), 6.97 (s, 1H), 6.91 (dt, 1H, $J = 9.0$, 2.4 Hz), 4.12 (t, 2H, $J = 6.4$ Hz), 2.81 (dt, 2H, $J = 7.5$, 0.9 Hz), 2.09 (s, 3H), 1.99 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.1$, 158.5, 156.1, 132.9, 127.5, 127.4, 123.0, 116.2, 115.9, 111.5, 110.3, 110.0, 103.6, 103.5, 62.8, 32.7, 21.2, 17.6 ppm; MS: $m/z = 235$ (M+).

3-(5-Chloro-1H-indol-3-yl)propyl acetate (**4e**, $C_{13}H_{14}ClNO_2$) Pale yellow oil; IR (KBr): $\bar{\nu} = 3572, 3427, 2925, 2854, 1688, 1462, 1227, 1099, 1056\,cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.05$ (br s, 1H), 7.65 (d, 1H, $J = 2.1$ Hz), 7.31 (d, 1H, $J =$ 2.3 Hz), 7.13 (m, 3H), 3.84 (t, 2H, $J = 6.1$ Hz), 2.83 (dt, 2H, $J = 7.8$, 1.0 Hz), 2.04 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.3$, 134.3, 128.1, 125.4,122.9, 122.2, 118.3, 114.7, 112.0, 62.3, 32.8, 21.2, 17.4 ppm; MS: $m/z = 252$ (M + 1).

3-(5-Bromo-1H-indol-3-yl)propyl acetate (**4f**, $C_{13}H_{14}BrNO_2$) Pale yellow oil; IR (KBr): $\bar{\nu} = 3498, 3375, 2978, 2891, 1734, 1458, 1022\,cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (br s, 1H), 7.63 (d, 1H, $J = 1.6$ Hz), 7.10 (m, 2H), 6.89 (s, 1H), 3.98 (t, 2H, $J = 6.4$ Hz), 2.77 (dt, 2H, $J = 7.9$, 0.8 Hz), 2.03 (s, 3H), 1.85 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.8$, 134.8, 129.5, 124.6, 122.8, 121.4, 115.7, 112.0, 111.8, 62.6, 32.2, 21.3, 17.3 ppm; MS: $m/z = 296$ (M + 1).

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References

1. a) Ihara M, Fukumoto K (1995) Nat Prod Rep 12:277; b) Saxton JE (1994) Nat Prod Rep 11:493; (c) Saxton JE (1983) Indoles. Wiley-Interscience, New York
2. Gribble GW (2000) J Chem Soc Perkin, Trans 1:1045
3. a) Gribble GW (1994) Contemp Org Synth 1:1; b) Hughes DL (1993) Org Prep Proc Int 25:607; c) Robinson B (1982) Wiley-Interscience, New York
4. a) Miyata O, Kimura Y, Muroya K, Hiramatsu H, Naito T (1999) Tetrahedron Lett 40:3601; b) Kissman HM, Farnsworth DW, Witkop B (1952) J Am Chem Soc 74:3948; c) Hegde V, Madhukar P, Madura JD, Thummel RP (1990) J Am Chem Soc 112:4549; d) Hillier MC, Marcoux JF, Zhao D, Grabowski EJJ, Mckeon AE, Tillyer RD (2005) J Org Chem 70:8385
5. a) Nakazaki M, Yamamoto K (1976) J Org Chem 41:1877; b) Ackermann L, Born R (2004) Tetrahedron Lett 45:9541; c) Baccolini G, Todesco PE (1981) J Chem Soc Chem Commun:563
6. a) Mhaske SB, Argade NP (2004) Tetrahedron 60:3417; b) Lipinska T, Guibé-Jampel E, Petit A, Loupy A (1999) Synth Commun 29:1349; c) Dhakshinamoorthy A, Pitchumani K (2005) Appl Catal 292:305; d) Zhu HP, Yang F, Tang J, He MY (2003) Green Chem 5:38
7. a) Zepeda LG, Morales-Rios MS, Joseph-Nathan P (1992) Synth Commun 22:3243; b) Shono T, Matsumura Y, Tsubata K (1984) J Org Chem 49:3711; c) Fischer GW (1995) J Heterocycl Chem 32:1557; d) Pete B, Bitter I, Szantay CJ, Schon I, Toke L (1998) Heterocycles 48:1139
8. Campos KR, Woo JCS, Lee S, Tillyer RD (2004) Org Lett 6:79