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Tetrahedron Letters 49 (2008) 3335–3340
Tetrahedron Letters

An expeditious and environmentally benign methodology for the synthesis of substituted indoles from cyclic enol ethers and enol lactones

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Received 19 September 2007; revised 11 February 2008; accepted 18 February 2008
Available online 10 March 2008

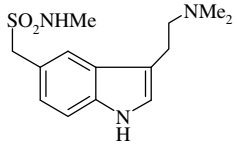
Abstract

A simple and environmentally friendly method is developed for the synthesis of substituted indoles from commercially available aryl hydrazines and cyclic enol ethers with Montmorillonite-K10 as a heterogeneous catalyst. The catalyst is non-toxic, inexpensive and recyclable and the process is clean, high yielding and operationally simple.

Keywords: Aryl hydrazine; Cyclic enol ether; Indole; Montmorillonite K-10

Indoles are an important class of compounds which have attracted considerable interest in recent years due to their therapeutic and pharmacological activities.[1–3] Substituted indoles are sometimes referred to as 'privileged structures' due to their high affinity towards many receptors.[4] For example, the neurotransmitter serotonin (5-hydroxytryptamine) is involved in various physiological functions such as appetite, sleep, body temperature and sexual behaviour.[5]

Numerous serotonin-like compounds, such as sumatriptan (**1**), avitriptan (**2**) and indomethacin (**3**) are well-known anti-migraine and anti-infammatory drugs.[6–8]



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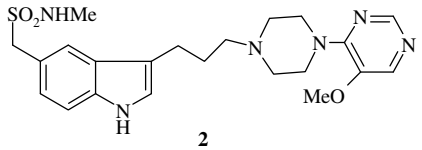

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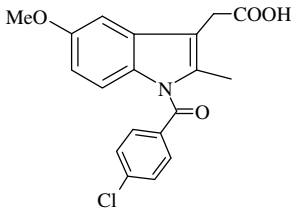

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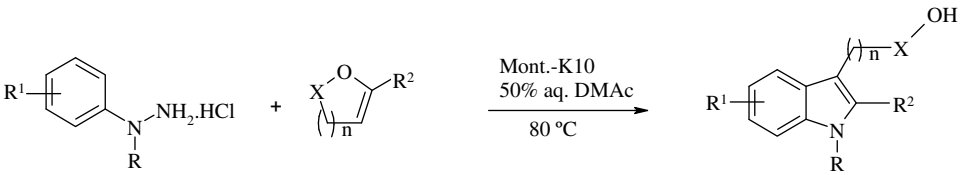
doi:10.1016/j.tetlet.2008.02.107



R^1 = H, CH_3, F, Cl, Br, COOH, OCH_3 n = 1,2 ; X= CH_2, C=O
R^2 = H, CH_3
(R = $PhCH_2$ when R^2 = CH_3 and X = CO, otherwise R = H)

Scheme 1.

Among the various approaches towards the synthesis of indoles,[9,10] the Fischer indole synthesis has maintained its prominent role. Further, the Fischer indole reaction with aldehydes or ketones often involves a two-step process, that is, hydrazone formation followed by cyclization and can result in low yields of products.[11–13] The reaction conditions range from warming with acetic acid to fusing with $ZnCl_2$, and refluxing with HCl/CH_3COOH, and PPA.[14–18] However, these catalysts are environmentally unfriendly, hazardous or difficult to handle and are also required in very large amounts (e.g., PPA in 8- to 9-fold excess by weight, $ZnCl_2$ in 3-fold excess).

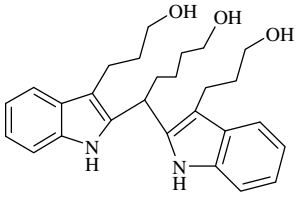
Campos has recently reported[19] the synthesis of substituted indoles from cyclic enol ethers, used as aldehydes equivalents, and enol lactones using 4% H_2SO_4 and dimethylacetamide (DMAc) as a co-solvent.

Thus, the discovery of a new, inexpensive and environmentally benign approach towards the synthesis of indoles continues. The use of clays as catalysts has gained significant interest in different areas of organic synthesis due to their environmental compatibility combined with good yields, reusability, non-corrosiveness, low cost, operational simplicity and the selectivities that can be achieved.[20–22]

Thus, herein we report a convenient and practical one-pot synthesis of 3-substituted indoles from commercially available cyclic enol ethers or enol lactones and aryl hydrazines using Montmorillonite K10 clay as catalyst (Scheme 1).

In our preliminary study, the reaction of phenylhydrazine hydrochloride with dihydropyran (DHP) was selected as a model reaction to test the activity of different heterogeneous Brønsted acidic catalysts—silica, Amberlyst-15, Amberlite-120, Indion-130, Montmorillonite K10 and zeolites-HY at 80 °C in 50% *N*,*N*-dimethylacetamide DMAc–H_2O for 3 h (Table 1).

It was found that Montmorillonite K10 was superior to all the other catalysts examined and gave a good yield of product. When we tried the same reaction in water as solvent, the product was obtained in only 50% yield. A significant amount of by-product **4** was formed.[19]



4

In a purely aqueous system, the product and dihydropyran were insoluble creating a highly concentrated 'organic layer' that resulted in increased formation of the triol by-product **4**. It was found that the addition of a co-solvent to the reaction decreased the formation of by-product to less than 5%. Encouraged by this result, we investigated the scope of this reaction in other polar solvents such as 50% aqueous acetonitrile, THF, DMF and DMAc (Table 2).

It was found that the reaction proceeded smoothly and gave an excellent 88% yield in 50% aq DMAc. To extend the scope of the reaction and to generalize the procedure, we investigated the reactions of a series of aryl hydrazine hydrochlorides with enol ethers such as DHP and DHF in the presence of Montmorillonite K10 at 80 °C in 50% aqueous DMAc (Table 3).

Table 1
Reaction of phenylhydrazine hydrochloride with dihydropyran in the presence of various solid acids[a]

Entry	Catalyst	Yield[b] (%)
1	Silica	25
2	Amberlyst-15	75
3	Amberlite-120	73
4	Indion-130	70
5	Montmorillonite K10	88
6	Zeolite-HY	52

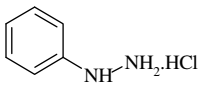
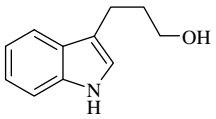
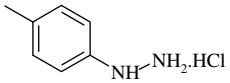
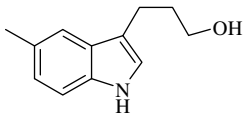
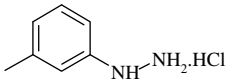
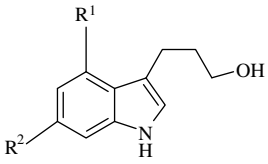
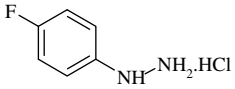
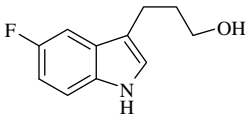
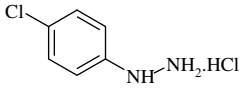
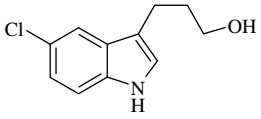
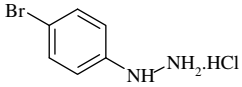
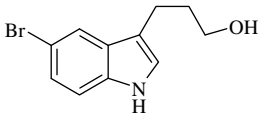
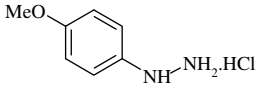
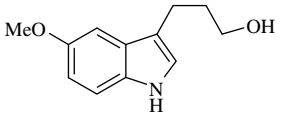
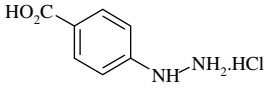
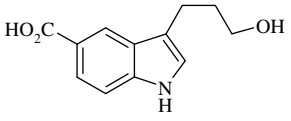
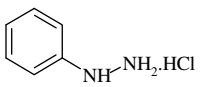
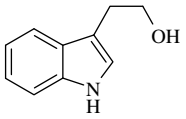
[a] Phenylhydrazine hydrochloride: 5 mmol, dihydropyran: 5 mmol, catalyst: 800 mg, solvent: H_2O: *N*,*N*-DMAc (1:1 v/v) 15 mL, reaction temperature 80 °C, 3 h.
[b] Isolated yield.

Table 2
Effect of solvent on the reaction of phenylhydrazine hydrochloride with dihydropyran in the presence of Mont. K10 at 80 °C[a]

Entry	Solvent	Yield[b] (%)
1	H_2O	50
2	H_2O–CH_3CN (1:1)	66
3	H_2O–*N*,*N*-DMAc (1:1)	88
4	H_2O–DMF (1:1)	75
5	H_2O–THF (1:1)	60

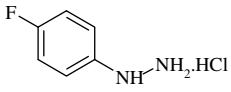
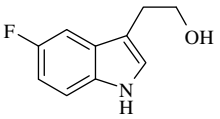
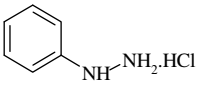
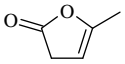
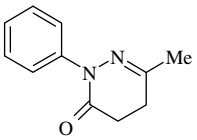
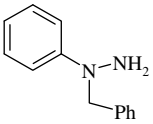
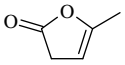
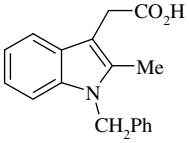
[a] Phenylhydrazine hydrochloride: 5 mmol, dihydropyran: 5 mmol, Mont. K-10: 800 mg, 3 h, solvent: 15 mL.
[b] Isolated yield.

Table 3
Synthesis of 3-substituted indoles from cyclic enol ethers or enol lactones using Mont. K10[a]

Entry	Aryl hydrazine	Enol ether/enol lactone	Time (h)	Product	Yield[b] (%)
1			3	 **3a**	88
2			1.5	 **3b**	90
3			2	 **3c**: R^1= H, R^2= Me **3d**: R^1= Me, R^2= H	70 **3c**:**3d** (55:45)[c]
4			1.5	 **3e**	83
5			2.5	 **3f**	68
6			2.5	 **3g**	70
7			1.5	 **3h**	80
8			3	 **3i**	65
9			2	 **3j**	75

(*continued on next page*)

Table 3 (*continued*)

Entry	Aryl hydrazine	Enol ether/enol lactone	Time (h)	Product	Yield[b] (%)
10			2	 **3k**	68
11			3	 **3l**	88
12			3	 **3m**	65

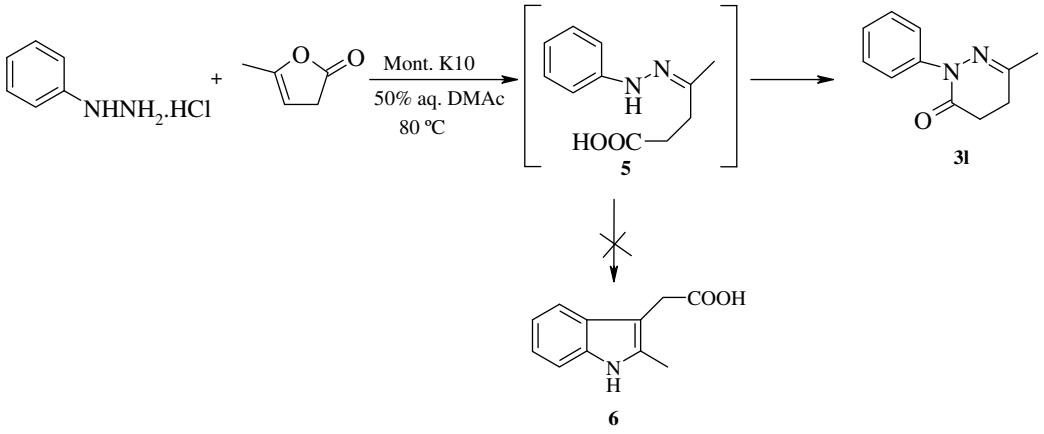
[a] All reactions were run in 50% aq DMAc at 80 °C.
[b] Isolated and unoptimised yields.
[c] Determined by ^{1}H NMR spectroscopy.

The reaction with *m*-tolylhydrazine hydrochloride led to the formation of a 55:45 mixture of regioisomeric indoles (entry 3). When the same procedure was employed on angelica lactone, the cyclic acyl hydrazone (**3l**) was the only observed product.[23] Formation of a cyclic acyl hydrazone could be possibly due to cyclization of acid hydrazone **5** rather than the expected 3,3-sigmatropic rearrangement to afford 2-methylindole 3-acetic acid (**6**) (Scheme 2). This could be successfully avoided by protecting the 1-NH of phenyl hydrazine with benzyl bromide[24] and subjecting *N*-benzyl phenylhydrazine to the same conditions, which afforded *N*-benzyl-2-methylindole acetic acid (**3m**) in 65% yield.

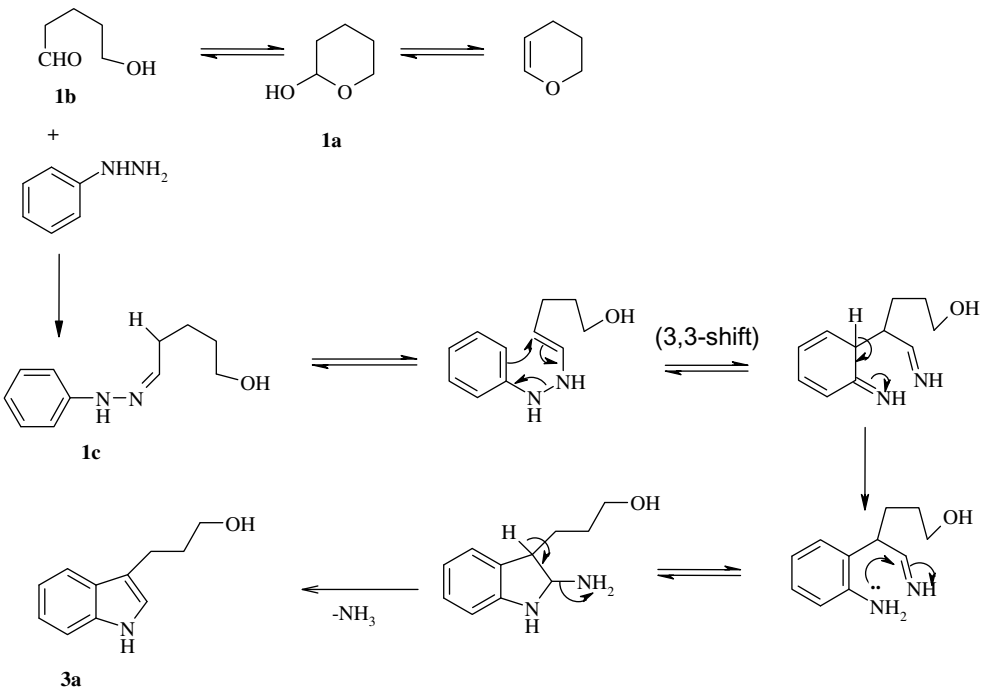
A tentative mechanism to rationalize the formation of the products is shown in Scheme 3. The cyclic enol ether can be hydrated easily in the presence of the acid catalyst in water to give **1a**[25,26] which then undergoes facile ring opening in water to produce **1b**. The condensation reaction between phenylhydrazine and **1b** generates hydrazone **1c**, which subsequently undergoes a 3,3-sigmatropic shift followed by a further rearrangement to give product **3a**.

The catalyst was recovered by filtration, washed with ethyl acetate, dried and recycled for use in subsequent reactions without significant loss in activity. For example, the reaction of phenylhydrazine hydrochloride and DHP under the present reaction conditions afforded, 86%, 88% and 83% yields of the corresponding indole over three cycles.

In summary, we have developed a simple and general method for the synthesis of substituted indoles, which offers several advantages including good to excellent yields,



Scheme 2.



Scheme 3.

use of an inexpensive and recyclable catalyst and cleaner reaction profiles.

Typical experimental procedure: To a mixture of phenylhydrazine hydrochloride (5 mmol) and Montmorillonite K-10 (800 mg) in 50% aqueous DMAc (15 mL) at 80 °C was added dihydropyran (5 mmol) dropwise over 1 min. The resultant reaction mixture was stirred at 80 °C or 3 h. The catalyst was then filtered off and the filtrate was extracted with ethyl acetate (5×2 mL). The combined organic layer was washed with water and concentrated. The crude product was purified by flash column chromatography (silica gel: 60–120 mesh and eluted with 20% ethyl acetate–petroleum-ether). All the products were fully characterized by comparison with authentic samples[19] and by elemental analysis and spectroscopic methods.

Representative data for compound **3a**, 3-(1*H*-indol-3-yl) propan-1-ol; IR (neat) 3544, 3412, 2937, 1458, 1339, 1229, 1054, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.05$ (br s, 1H), 7.58 (d, 1H, $J = 7.8$ Hz), 7.26 (d, 1H, $J = 7.8$ Hz), 7.15 (t, 1H, $J = 7.5$ Hz), 7.08 (t, 1H, $J = 7.2$ Hz), 6.8 (s, 1H), 3.65 (t, 2H, $J = 6.4$ Hz), 2.8 (t, 2H, $J = 7.5$ Hz), 2.01 (m, 2H); MS (EI, 70 eV) m/z, 175 (M^+), 130 (100), 77 (15). Anal. Calcd for $C_{11}H_{13}NO$: Calcd: C, 75.43; H, 7.43; N, 8.00. Found, C, 75.40; H, 7.45; N, 8.03.

Acknowledgement

P.R.S. thanks the CSIR, New Delhi, for the award of a fellowship.

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