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Tandem Wittig – Reductive annulation decarboxylation approach for the synthesis of indole and 2-substituted indoles

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ABSTRACT

A simple tandem Wittig reaction-reductive decarboxylation route is established for the synthesis of indoles from commercially available *o*-nitrobenzaldehydes and a stable phosphorane. The method allows access to indoles in a very fast manner without involving any metal or expensive reagents or inert atmosphere. Also 2-substituted indoles are obtained which forms an important core of many biological active compounds.

Introduction

The indole ring constitutes large percentage of naturally occurring heterocyclic compounds. It is of immense interest to medicinal chemist due to its usage in synthetic pharmaceuticals such as antimicrobial, antibacterial, anti-inflammatory, antitumor, anticancer etc.[1] Due to this indole scaffold has become target of research for developing methodologies and large number of methods have been accomplished. Synthesis of indole has been reviewed several times.[2] Recently several powerful strategies utilizing metal catalysed cross coupling reactions have been developed for this ring system. Very recently C—H functionalisation has attracted much interest amongst synthetic organic chemist.[3,4] The C—H insertion through nitrene intermediates[2g] was developed by Cadgon, Sundberg and Hessienberger.[5] Cadgon's initial studies indicated triethyl phosphite to be better reagent for the reductive cyclisation leading to carbazoles. Mali et al. showed that the yield to 2-carboethoxy indole increases when fivefold excess of triethyl phosphite was used. From our laboratory use of triphenylphosphine in refluxing diphenyl ether was reported for the synthesis of 2-acyl indoles.[6] The formation side product *N*-ethyl indole in case of triethyl phosphite mediated reaction is avoided using triphenylphosphine. Later Freener et al. refined this reaction using refluxing *o*-dichlorobenzene.[7] Subsequently Sanz et al. developed a much milder procedure in refluxing toluene using dioxomolybdenium catalyst.[8] However, the latter two procedures requires much longer time (16–18 h).

These reactions can be run in much shorter time if carried out under microwave reactors.[9] Palladium catalysed reductive cyclisation using carbon monoxide is also known to be effective way of construction of indole nucleus.[10] Continuing our interest in reductive cyclisation for the synthesis of nitrogen heterocycles,[11] we report herein one pot method for the synthesis of 2,3-unsubstituted indoles, and 2-alkyl indoles using stable Wittig reagents. These 2-alkyl indoles find their presence in many of the bioactive frameworks, for example oxypertine **A** is an antipsychotic agent, indomethacin[10] **B** is a nonsteroidal antiinflammatory agent and paraadoline **C** is an alazaric agent (Fig. 1).[1d]

Results and discussion

Indoles and 2-substituted indoles can be conveniently prepared by 2-step synthesis using Cadgon's method or by other reductive cyclisation[5,12] methods wherein first 2-vinyl nitrobenzene is prepared from 2-nitrobenzaldehydes via appropriate unstable Wittig reagent or other reagents under anhydrous conditions in inert atmosphere and then are reductively cyclised to get the parent indole in 25–55% yield (Scheme 1).

We were interested in developing reactions condition which does not involve the problem of handling unstable Wittig reagents

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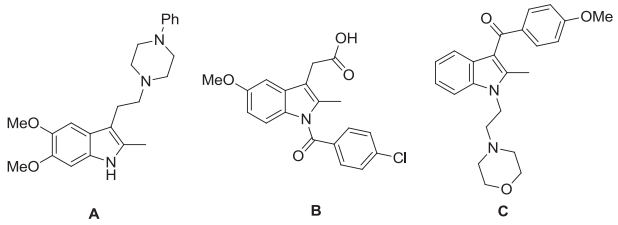
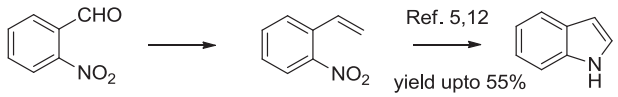


Fig. 1. Drugs containing 2-methyl indole.

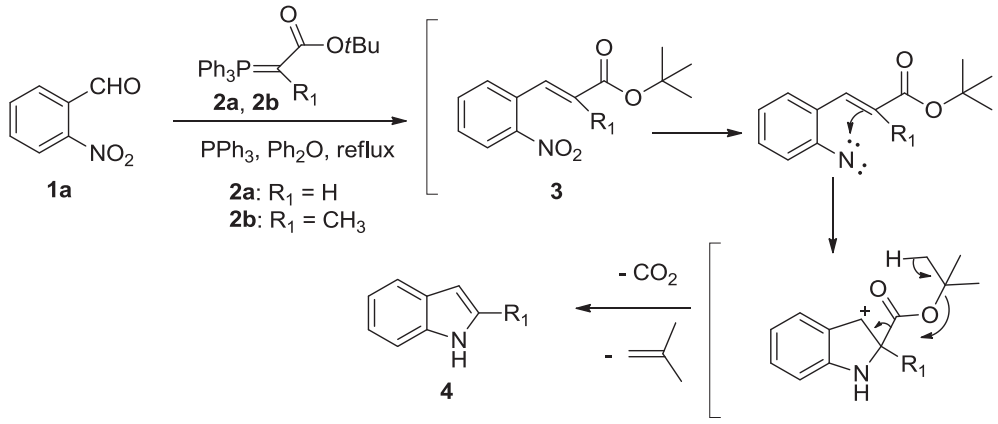


Scheme 1. Literature synthesis.

and get the product in a single step. In order to do that we thought that if we use appropriate stable phosphorane **2**, we may be able to achieve Wittig reaction, reductive cyclisation, hydrolysis and decarboxylation in one pot as shown in Scheme 2.

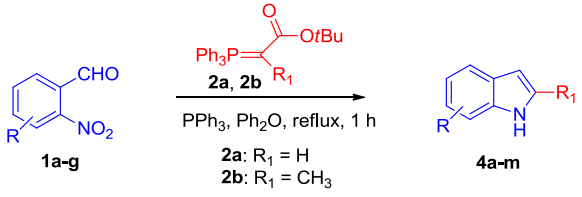
To test the hypothesis, a mixture of *o*-nitrobenzaldehyde **1a** (1 equiv), phosphorane **2a** (1 equiv) and triphenylphosphine (2.4 equiv) were refluxed in diphenyl ether for 1 h. Usual workup provided parent indole **4a** in 66% yield (Table 1, entry 1).

After confirming that the required product could be obtained by the reaction conditions reported from our laboratory,[6] we evaluated the other reaction conditions employed for reductive cyclisation known in literature (Scheme 3). Cadgon's method in refluxing triethyl phosphite showed complete conversion of starting in just 30 min, resulting in ester **5a** in 68% yield. The same result was obtained in refluxing xylene in presence of triethyl phosphite. Sanz's condition with molybdenum catalyst also provided ester **5a** in comparatively lower yield. Freemen's method for nitrene formation with triphenylphosphine in refluxing *o*-dichlorobenzene



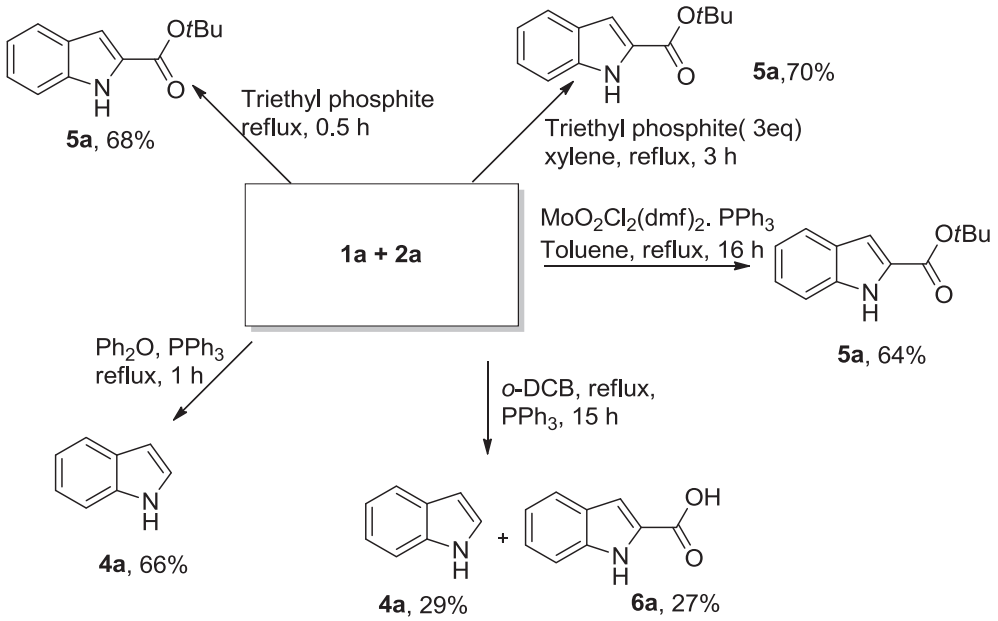
Scheme 2. Retrosynthetic pathway.

Table 1
One pot synthesis of indoles.



Sr. No.	R	1	R_1, R	4	Yield%[a]
1	H	**1a**	H, H	**4a**	66
2	5-Cl	**1b**	H, 5-Cl	**4b**	50
3	5-Br	**1c**	H, 5-Br	**4c**	46
4	5-OMe	**1d**	H, 5-OMe	**4d**	51
5	4,5-OMe	**1e**	H, 5,6-OMe	**4e**	52
6	4,5,6-OMe	**1f**	H, 4,5,6-OMe	**4f**	62
7	4,5-OCH_2O	**1g**	H, 5,6-OCH_2O	**4g**	45
8	H	**1a**	CH_3, H	**4h**	43
9	5-Cl	**1b**	CH_3, 5-Cl	**4i**	47
10	5-Br	**1c**	CH_3, 5-Br	**4j**	45
11	5-OMe	**1d**	CH_3, 5-OMe	**4k**	48
12	4,5-OMe	**1e**	CH_3, 5,6-OMe	**4l**	47
13	4,5-OCH_2O	**1g**	CH_3, 5,6-OCH_2O-	**4m**	36

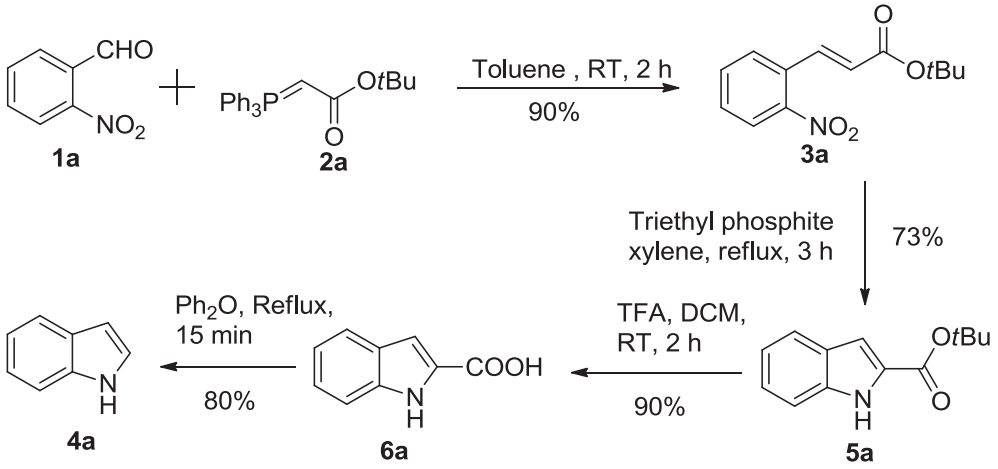
[a] Isoated yields.



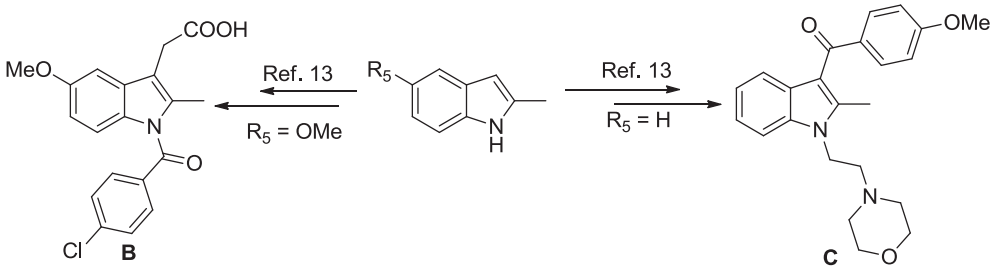
Scheme 3. One pot Wittig reductive cyclisation studies.

resulted in mixture of indole **4a** and indole-2-carboxylic acid **6a** in 29% and 27% yield respectively. As in none of the above cases we could get the required parent indole except partly in the last method we chose our protocol for further studies.

The isolation of acid **6a** under Sanz's condition suggested that in our one step protocol the corresponding ester **5a** is formed first which then undergoes hydrolysis followed by decarboxylation and not via decarboxylative reductive cyclisation as proposed in Scheme 2. Hence, we compared the yield of one pot protocol with step wise reaction sequence with isolation product at every step (Scheme 4). Cinnamate ester **3a** was isolated in 90% yield; reductive cyclisation of **3a** with triethyl phosphite in xylene gave indole ester **5a** in 73% yield. Hydrolysis of the ester with trifluoroacetic acid and decarboxylation at high temperature fetched the acid **6a**



Scheme 4. Stepwise approach.



Scheme 5. Application to bioactive compounds.

and the indole **4a** in 90 and 80% yield respectively. The overall yield of the stepwise sequence was found to be 47% and required three chromatographic purification steps.

As the one pot protocol gave better yield in shorter reaction time, this protocol was then explored on variety of nitrobenzaldehydes to fetch the corresponding indoles (Table 1). Nitrobenzaldehydes with one, two and three methoxy groups were easily converted to its corresponding indole derivatives in moderate yield. The method was then successfully extended to synthesize 5-chloro and 5-bromo indoles in 50 and 46% yields respectively, which can be potentially exploited for further functionalisation of indole nucleus. For the synthesis of 2-methyl indoles phosphorane **2b** was required. This was synthesized by alkylating **2a** with methyl iodide. Following the same protocol the phosphorane **2b** was reacted with nitroaldehydes **1a**–**e**, **1g** to fetch all important 2-methyl indole derivatives in slightly lower yields than the corresponding unsubstituted indoles. Lower yields of 2-alkyl indoles were attributed to their higher reactivity. The 2-methyl indoles are important starting intermediates for preparing pharmaceutically active compounds (Scheme 5).[13]

Conclusions

In conclusion a practical metal free synthesis of indole and 2-methyl indoles in one pot from easily available substituted o-nitrobenzaldehydes and stable phosphoranes was achieved. The reactions involved in this one step protocol are Wittig reaction, reductive cyclisation, hydrolysis and decarboxylation. The important feature of this methodology is its ease of handling of substrates, short reaction time and no requirements of inert atmosphere.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.04.001.

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