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An efficient synthesis of medicinally important indole based triarylmethanes by using propylphosphonic anhydride (T3P®)

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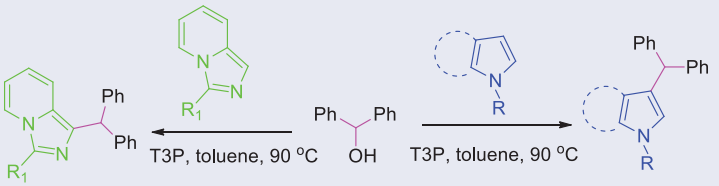
ABSTRACT

We have developed an economical and efficient method for the synthesis of medicinally and synthetically important indole-based triarylmethanes by using indoles and benzhydrols in the presence of propylphosphonic anhydride (T3P®). This methodology is an alternate approach for the C–C bond formation with good to excellent yields. In this T3P-mediated dehydration approach, the by-product is highly soluble in water, so that it can be done at larger scale also. In addition to that this efficient protocol has several advantages such as mild reaction conditions, short reaction time and operational simplicity. We have successfully synthesized pyrrole, imidazothiadiazole and imidazolo pyridine based triarylmethanes also.

GRAPHICAL ABSTRACT



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KEYWORDS
Alcohols; nitriles; N-substituted amides; propylphosphonic anhydride (T3P®); solvent-free condition

Introduction

Triarylmethane frameworks belong to a class of bioactive molecules, which are widely featured in dyes,[1] material sciences,[2] medicinal chemistry,[3] bio-organic chemistry,[4] natural products and pharmacologically important compounds.[5] For example, GPR40 modulator (I) has emerged as a promising pharmacological agent for treating diabetes,[6] compound II represents a potential antituberculotic activity, Letrozole, Vorozole and compound (V) are potent non-steroidal aromatase inhibitors, compound

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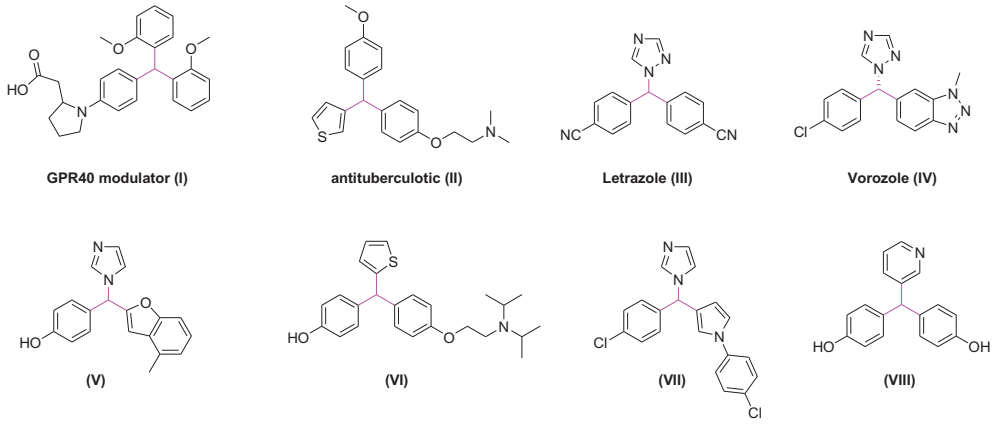


Figure 1. Biologically active triarylmethanes.

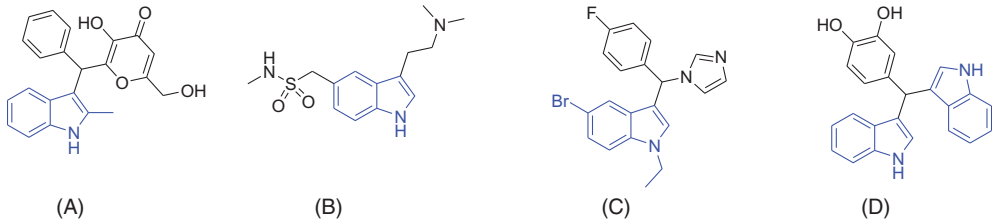


Figure 2. Bioactive indole derivatives.

(VI) is a potent antitubercular, compounds (VII) and (VIII) are potent antifungal and antiviral agents, respectively (Fig. 1).[7] Owing to their unique structural properties and potential applications in drug discovery and functional material design, the synthesis of triarylmethanes has received continuous attention from the chemistry community.[8]

Among heterocyclic compounds, indoles are privileged and found in many natural products and also as pharmaceutical agents due to their vast biological activities. Especially 3-substituted indole derivatives are building blocks of many promising therapeutic agents such as analgesic,[9] antiviral,[10] antibacterial,[11] potent kinase inhibitors[12] and hypoglycemic. The below compounds (Fig. 2) are the bioactive indole derivatives, compound (A) is a potent antifungal and antibacterial agent,[13] compound (B) called Sumatriptan is used for the treatment of migraine headache,[14] compound (C) is an aromatase inhibitor against breast cancer[15] and compound (D) functions as HIV-1 integrase inhibitor.[16]

The bioactivity of 3-substituted indoles encouraged us to synthesize 3-(bis(aryl)-methyl)-1H-indole and different catalytic strategies have been reported by different groups using Lewis acids,[17] Brønsted acids[18] or transition metal complexes as catalysts. Huanrong et al. reported iron catalyzed C–C bond activation with 1,3-dicarbonyl units as leaving groups,[19] Debjit et al. reported palladium(II)-catalyzed efficient C-3 functionalization of indoles with benzylic and allylic alcohols.[20] Hidemasa et al. reported gold-catalyzed direct substitution of benzyl alcohols with various nucleophiles provides methodology for the formation of C–C and C–N bonds,[21] Kobayashi and coworker reported DBSA-catalyzed dehydrativenucleophilic substitutions of alcohols in

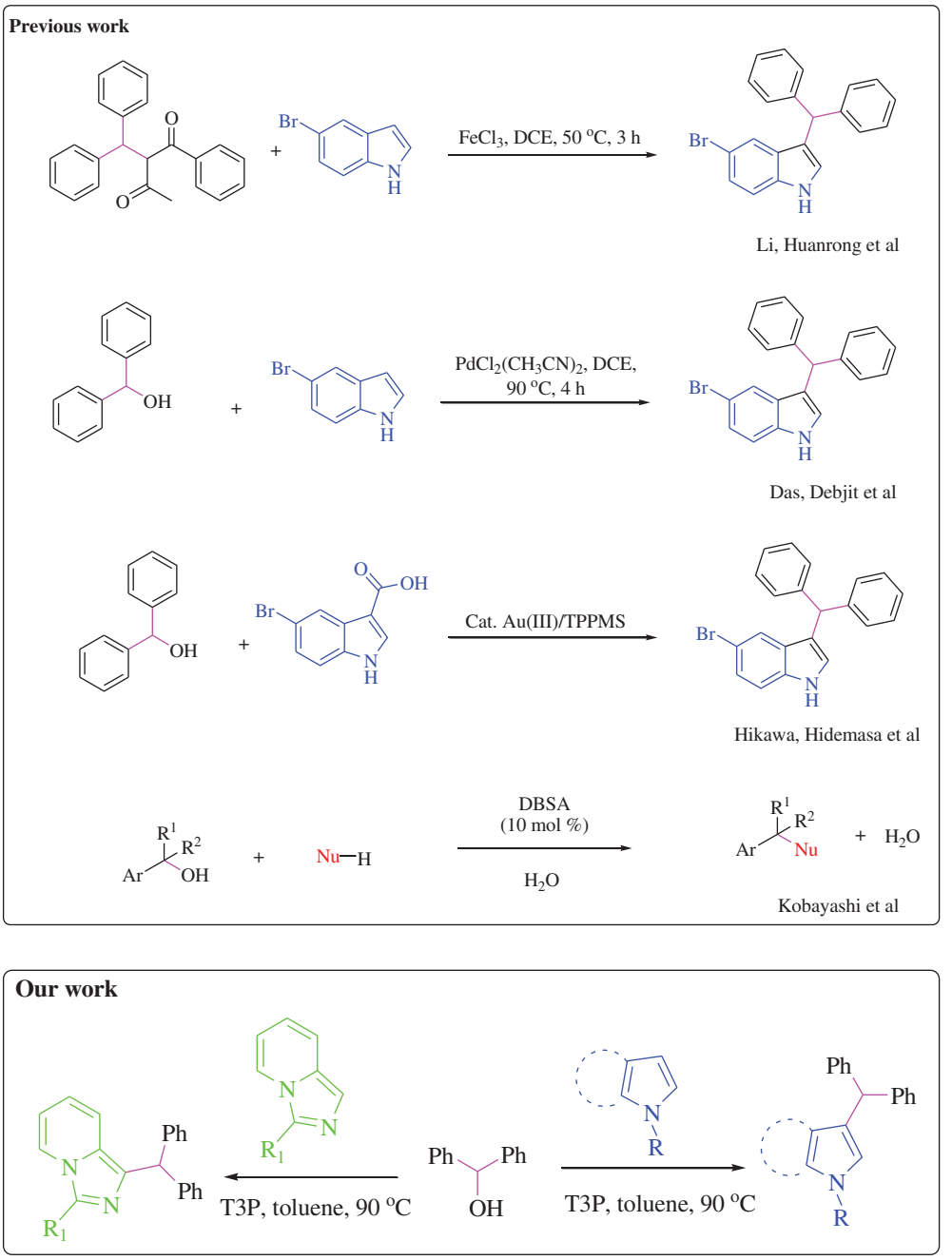
water.[22] Likewise different groups reported different catalytic strategies using Lewis acids,[17] Brønsted acids[18] or transition metal complexes as catalysts. However, these methods suffers from significant limitations like limited substrate scope, as contamination of metals with desired product, low yields, harsh reaction conditions and expensive reagents. Hence, new methods for indole functionalization continue to attract more attention.

However, to the best of our knowledge, no examples of T3P inter molecular dehydrative alkylation of indoles with alcohols have been previously described.[23] In this context, it is highly essential to develop novel approach of dehydrative reactions of alcohols for the construction of triarylmethane scaffolds in accordance with environmental friendliness. Besides, the dehydration of alcohols has been considered as having high atom and step-economy. In continuation of our interest in the applications of T3P,[24] cycloaddition reactions[25] and synthesis of heterocyclic compounds,[26] we explored a novel approach to access triarylmethane frameworks using T3P (Scheme 1), which having wide application in the field of synthetic organic chemistry because of its excellent reaction selectivity, less toxicity, low epimerization character, less allergenic and broad functional group tolerance.[27]

Results and discussion

The reaction of un-substituted indole **1a** with benzhydrol **2a** was selected as the model reaction to establish the best reaction condition. Initially, the reaction was carried out in the absence of T3P at reflux condition; the desired product did not form (Table 1, entry 1). The feasibility of the reaction was checked by using indole **1a** (1 equiv.) with benzhydrol **2a** (1 equiv.) using T3P® (25 mol%) in the presence of toluene as a solvent at 90 °C (Table 1). Pleasantly, required product **3a** obtained with 20% yield after 14 h (Table 1, entry 2). Inspired by this result, the amount of T3P was increased from 25 mol% to 50 mol% and 100 mol%, surprisingly complete consumption of starting materials were observed with 100 mol% and the product **3a** was isolated in 85% yield (Table 1, entries 3 and 4). Further increasing the amount of T3P from 100 mol% to 125 mol% no significant improvement was observed (Table 1, entry 5), thus T3P loading was optimized at 100 mol%. In order to improve the results, solvent was changed from toluene to xylene and 1,4-dioxane (Table 1, entries 6 and 7) and could not get better results. In addition to this, various solvents like THF and DMF were also tried, but only trace amount of product was observed (Table 1, entries 8 and 9). Further reaction was performed by using water as a solvent and also under solvent-free condition but there was no product (Table 1, entries 10 and 11). With continuous interest, the effect of temperature was also tested by a decrease and increase of temperature from 90 °C to 80 °C & 100 °C (Table 1, entries 12 and 13), and we could not find better results. Finally, we found that reactions of **1a** with **2a** in the presence of T3P (1 equiv. or 100 mol%) at 90 °C for 14 h was ideal (Table 1, entry 4).

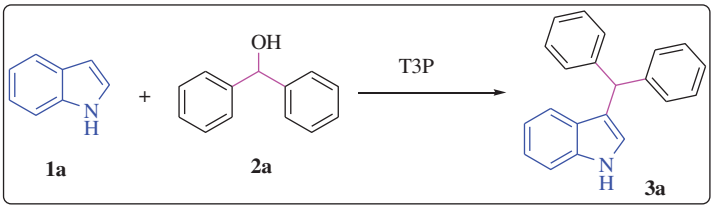
With the above optimized reaction conditions, the efficiency and versatility of this newly developed approach was generalized using a variety of substituted indoles, heterocyclic compounds and various benzhydrols, the results are summarized in Scheme 2. Thus, the developed methodology preceded smoothly using 100 mol% of T3P with a



Scheme 1. Benzylation of heterocycles using benzhydrol and T3P.

variety of substituted benzhydrols, like methyl, fluoro and chloro, in all the cases reaction went smoothly. Further, the influence of substituents on the heterocycles like indoles, pyrroles, imidazothiadiazoles and imidazolo pyridines was also investigated, both electron donating and electron withdrawing groups have found to be compatible to give the desired products with an excellent yields.

Table 1. Optimization of reaction conditions.



Entry	Solvent	T3P (mol%)	Temp (°C)	Time (h)	Yield (%)
1	Toluene	–	Reflux	24	–
2	Toluene	25%	90	16	20
3	Toluene	50%	90	16	44
4	**Toluene**	**100%**	**90**	**14**	**85**
5	Toluene	125%	90	14	82
6	Xylene	100%	90	14	45
7	1,4-Dioxane	100%	90	14	57
8	THF	100%	80	14	Trace
9	DMF	100%	90	14	Trace
10	Water	100%	90	14	NR
11	No solvent	100%	90	14	20
12	Toluene	100%	80	14	70
13	Toluene	100%	100	14	75

Reaction condition: **1a** (1.0 equiv.) and **2a** (1.0 equiv.) in the presence of T3P® (1.0 equiv., 50% in ethyl acetate) in toluene at 90 °C for 14 h.
The bold values are represent the best optimized condition obtained for synthesis of compounds.

The mechanism for the benzylation of heterocycles was proposed and shown in Scheme 3. In the first step, activation of **1a** takes place when lone pair of electrons on the oxygen atom of **1a** attacks on **A** (T3P) to form an intermediate **B** and secondly, intermediate **B** was attacked by indole **2a** to form intermediate **D** by eliminating the by-product open hydrated T3P which is **C**. The intermediate **C** abstracts hydrogen from intermediate **D** followed by re-aromatization of indole takes place to give **3a** as a product with the expulsion of intermediate **E**.

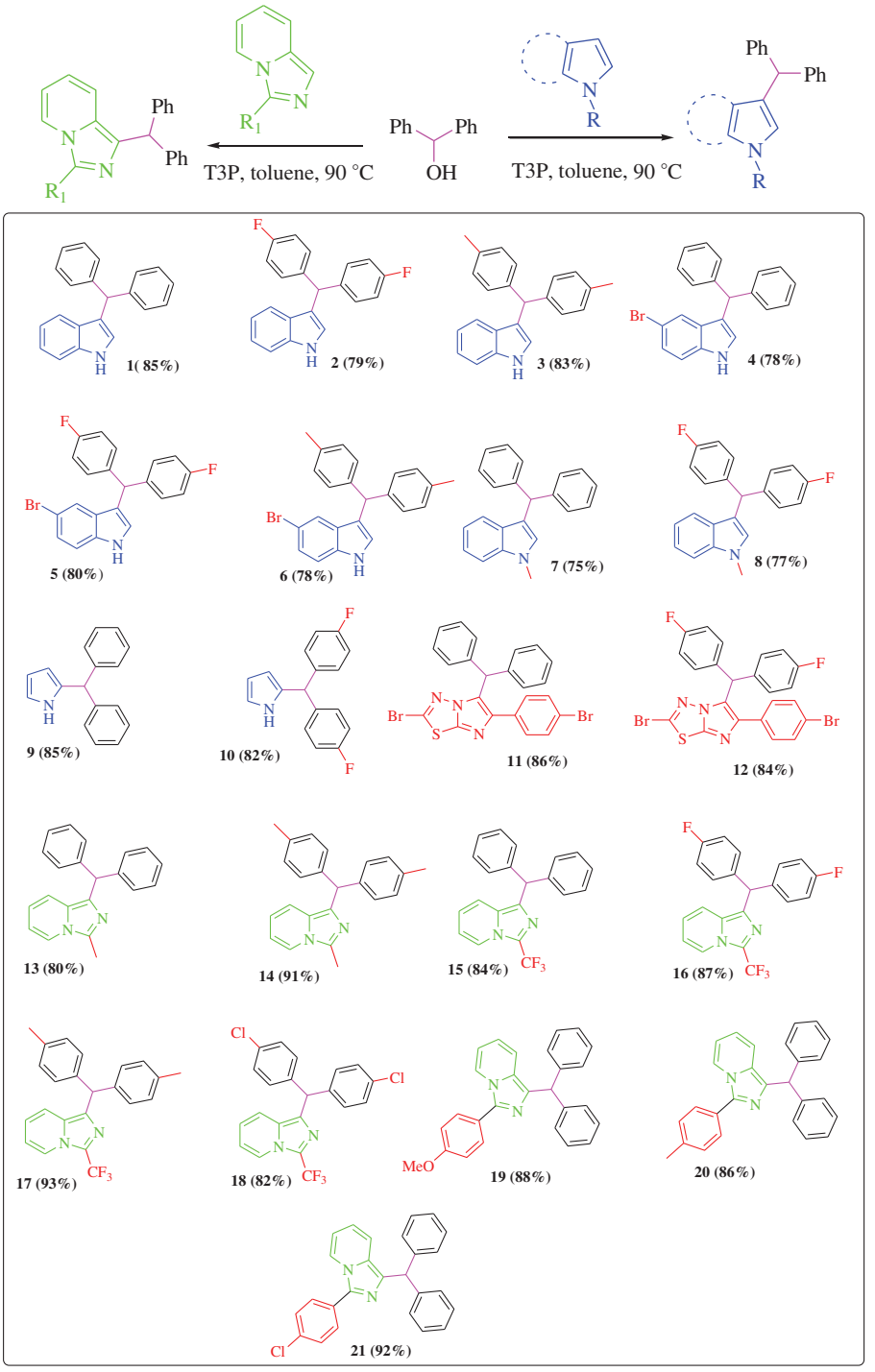
Conclusion

In conclusion, we have developed an efficient T3P-mediated dehydrativebenzylation method for the synthesis of medicinally and synthetically important indole-based **triarylmethanes** by using indoles and benzhydrols. Along with indole derivatives; pyrrole, imidazothiadiazole and imidazolo pyridine based triarylmethanes were also successfully executed. The obtained scaffolds are of high interest due to their potential biological and pharmaceutical activity.

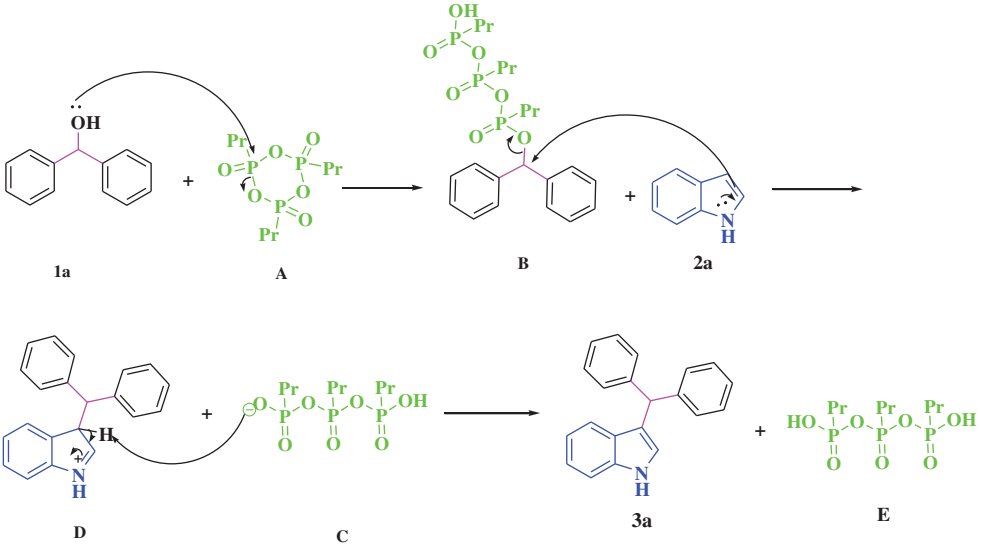
Experimental procedure

Materials and methods

All work relating to analytical thin layer chromatography were performed with E. Merck silica gel 60F254 aluminum plates and were visualized with UV light. The following mobile phases were employed for TLC: chloroform, methanol, hexane and ethyl acetate in different ratios. The instrumental techniques employed for the



Scheme 2. Substrate scope of reactions.



Scheme 3. Plausible mechanism.

characterization of the newly synthesized compounds include ^{1}H NMR, ^{13}C NMR and mass spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-AV (500, 400 and 126, 101 MHz, respectively) and Agilent WM (400 and 100 MHz) Fourier transforms spectrophotometer in CDCl3 or DMSO-d6 solution using tetramethylsilane (TMS) as internal standard. Chemical shifts were recorded in ppm relative to TMS. Mass and purity were recorded on an LC–MSD-Trap-XCT (Agilent Technologies Inc.). All the reagents and chemicals used were from Sigma Aldrich chemicals.

General procedure

To a stirred solution of alcohol (1 equiv.) and hetero cyclic compound (1 equiv.) in toluene (20 vol.) was added T3P reagent (1 equiv.) at room temperature. The reaction mixture was heated to 90 °C for 14 h. The reaction was monitored by TLC till completion of starting material. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with sodium bicarbonate (10%) solution, water followed by brine solution. The organic layer was dried over sodium sulfate and concentrated under reduced pressure; the crude product was purified by column chromatography to afford the desired compound.

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(L1)/2017-18/GRD-681/79/2018-2019] dated: 17/09/2018; and Minor Research Project U.O. [NO: DV6/375/MRP/2017-18], dated: 12/02/2018 is gratefully acknowledged.

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