Journal of the Korean Chemical Society
2012, *Vol. 56, No. 1*
Printed in the Republic of Korea
http://dx.doi.org/10.5012/jkcs.2012.56.1.074

Quick Access to Bis(indolyl)methanes: T3P as a Novel Catalyst System

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(Received May 29, 2011; Accepted November 30, 2011)

ABATRACT. A new catalytic system has been developed in the synthesis of bis(indolyl)methanes using cyclic phosphonic acid anhydride(T3P). Short reaction time, simplicity of isolation, safe catalyst and high yields of product are the features.

Key words: T3P, Indole, Aldehydes, Ketones, Bis(indolyl)methanes

INTRODUCTION

Indole and its derivatives are important from the point of chemistry and physiological and pharmacological properties.[1] The broad spectrum of biological properties exhibited by indole and its derivatives include antibacterial, antibiotic, cytotoxic, antioxidative, insecticidal and antiinflamatory activities.[2] Bis(indolyl)methanes are a class of indole derivatives produced by the eletrophilic reaction of indole with aldehydes and ketones are known to promote estrogen metabolism in both women and men and are expected to have an application in the prevention of breast cancer.[3] A few bioactive members of this class like Vibrindole-A and others have also been isolated from natural sources and are found to be pharmaceutically important.[4] Huge number of publications available in literature show the research interest from chemists and biologists in developing protocols to synthesize these compounds because of the interesting biological properties and other uses.[5] The methods employed for the synthesis of this class of compounds include, the reaction of indole with an aromatic or aliphatic aldehyde or a ketone in presence of suitable Lewis acid or Brönsted acid catalyst such as $InCl_3$ or $In(OTf)_3$,[6] $Ln(OTf)_3$,[7] $LiClO_4$,[8] VCl_3,[9] $CuBr_2$,[10] trichloro-1,3,5-triazine,[11] zeolite[12] and molecular iodine.[13] The use of sulphamic acid,[14] polyindole salt,[15] silica- supported sodium hydrogen sulfate and amberlyst-15,[16] rare-earth perfluorooctanoate [$RE(PFO)_3$],[17] diphosphooctadecatungstic acid[18] and ionic liquid[19] has been documented. Other methodologies like microwave/silica chloride[20] and ultrasound/CAN are also utilized.[21]

However, the yields of some examples are not satisfactory and the methods mentioned usually involve expensive reagents, relatively harsh conditions, and longer time durations are required for completion of the reaction. Developing suitable alternatives which exclude the above limitations are a welcome goal and herein we explore T3P as a new catalyst for the synthesis of bis (indolyl) methanes.

Propylphosphonic anhydride(T3P) is an highly reactive n-propyl phosphonic acid cyclic anhydride, generally used as coupling agent and water scavenger with low toxicity and low allergenic potential.[22] Broad functional group tolerance, low epimerization tendency, easy work up due to water soluble byproducts make the reagent one among the potential class of reagents for diverse transformations.[23]

EXPERIMENTAL

All the chemicals used are of commercial grade and were used without further purification. The products were characterized by comparison of their physical, IR, ^1H NMR, and LC-mass spectra with those reported in the literature and novel compounds by their spectral analysis.

General procedure for the preparation of bis (indolyl) methanes

A mixture of Indole (5 mmol), aldehyde (2.5 mmol) or ketone (2.5mmole), T3P (10 mole %) taken in dry dichloromethane (MDC) and stired for appropriate time (*Table* 2). The progress of reaction was monitored by TLC. After the reaction is over the precipitated product filtered from reaction mixture, washed with cold MDC and dried to get the pure product.

Selected spectral data

Compound 3a: Solid; mp-Found, 210-213 ºC; IR (KBr, ν cm^{-1}): 3480, 2973, 1631, 1599, 1498, 1031, 779. ^1H NMR (400 MHz, $CDCl_3$): *d* 2.04 (t, 2H), 2.76 (t, 4H), 3.80 (s,

6H), 7.38 (dd, 4H, *J*=7.6 Hz), 7.29 (s, 2H), 7.96 (s, 2H), 11.23 (s, 2H), ^{13}C NMR (DMSO) δ 24.7, 26.3, 43.1, 110.0, 111.2, 118.6, 121.5, 120.7, 121.8, 132.6, 135.5. MS: *m*/*z*= 403.44 (M^+).

Compound 3b: Semisolid; IR (KBr, ν cm^{-1}): 3474, 2977, 1638, 1591, 1492, 1038, 771.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (t, 2H), 2.75 (t, 4H), 6.8 (d, 2H, *J*=2.4Hz), 6.95 (d, 2H, *J*=2.1Hz), 7.22 (d, 2H, =2.8Hz), 7.59 (s, 2H), 10.84 (s, 2H), ^{13}C NMR (DMSO) δ 24.1, 26.1, 43.1, 111.0, 117.2, 119.6, 120.5, 120.7, 120.8, 131.6, 134.5. MS: *m*/*z*= 323.35 (M^+).

Compound 3c: Solid; IR (KBr, ν cm^{-1}): 3477, 2971, 1639, 1590, 1491,1474 1092, 1033, 772.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.8 (s, 6H), 7.2 (m, 5H), 7.5 (m, 6H), 8.1 (s, 2H, *J*=2.8Hz), 11.3(s, 2H), ^{13}C NMR (DMSO) δ 23.1, 27.1, 42.1, 110.0, 116.2, 118.6, 121.5, 122.7, 121.8, 132.6, 133.5. MS: *m*/*z*=471.49 (M^+).

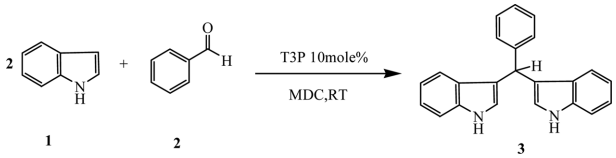
Compound 3d: Liquid; IR (KBr, νcm^{-1}): 3467, 2981, 1649, 1580, 1481,1484 1082, 1023, 762.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03 (m, 2H), 3.72 (t, 4H, *J*=1.6Hz), 3.78 (s, 6H), 6.81 (t, 2H, *J*=0.8Hz), 7.01 (t, 2H, *J*=1.2Hz), 7.29 (d, 2H *J*=8.4Hz), 7.36 (d, 2H *J*=8.0 Hz), 7.39 (s, 2H), ^{13}C NMR (DMSO) δ 22.1, 28.1, 43.1, 111.0, 114.2, 116.6, 120.5, 126.7, 123.8, 135.6, 138.5. MS: *m*/*z*=315.42 (M^+).

Compound 3i: Solid; mp-Found, 100-101 ºC; Reported: 9496 ºC. IR (KBr, ν cm^{-1}): 773, 1061, 1218, 1528, 1619, 2944, 3420. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 5.81 (s, 1H), 6.68 (s, 2H), 6.93 (t, 2H, *J*=7.5 Hz), 7.6 (d, 2H, *J*=7.3 Hz), 7.197.26 (m, 6H), 7.29 (d, 2H, *J*=7.3 Hz), 7.91 (br, 2H). ^{13}C NMR (DMSO) δ 21.9, 43.6, 110.3, 113.2, 118.7, 121.6, 122.7, 123.9, 127.2, 129.0, 129.3, 132.8, 135.5, 136.7. MS: *m*/*z*=336 (M^+).

RESULTS AND DISCUSSIONS

In view of developing novel and quick access to bis (indolyl) methanes herein we would like to report a simple, efficient and rapid method for the synthesis of bis (indolyl) methanes (*Scheme* 1). It was found that T3P is an effective promoter for the synthesis of bis (indolyl) methanes by the reaction of indoles and substituted indoles with aryl, heteroaryl, and aliphatic aldehydes at room temperature. In order to get the best experimental conditions Indole **1** and benzaldehyde **2** (in 2:1 molar ratio) in the presence of 20 mol% of T3P stirred at room temperature and the course of the reaction was monitored by thin layer chromatography.Interstingly both the reactants disappeared within 30 min and the product formed in 79% as indicated by LCMS analysis. Isolation after aqueous workup and chromatography on silica gel gave the required product in 70% as white solid. Encouraged by the result we carried out the same reaction in different solvents to see whether higher conversions can be achieved. The results are tabulated (*Table* 1). When we carried out the reaction in MDC an interesting observation came out. Exactly after 15 min pure product precipitated from the reaction mixture and the yield was as high as 92% which avoided column purification. So MDC came out to be the best solvent and for further optimization studies MDC was selected as solvent. Different concentrations of catalyst like 20, 15, 10 and 5 mole% were tried and product formed in 80, 92, 93 and 62% yield respectively. This indicates that 10 mol% of T3P is sufficient for the best result (*Table* 1, Entry 2).

To establish the generality of the method various aldehyde and ketones with different substituents with varied electronic nature tried and the products were obtained in excellent yields. Good yields were obtained even when heterocyclic and aliphatic aldehydes (*Table* 2, Entries **g** & **j**) were employed and when differentially substituted indoles were used (*Table* 2, Entries **a** to **d**) the yields were not less than 90%. The beauty of the methodology is further increased when strained cyclic ketone viz cyclobutanone was used as the ketone component with excellant yield.



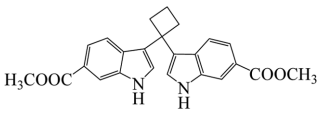
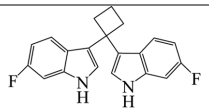
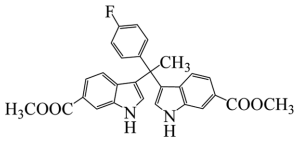
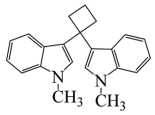
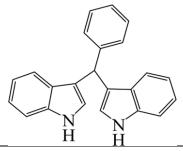
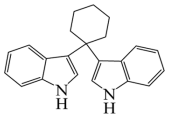
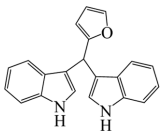
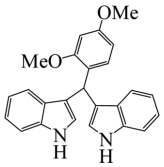
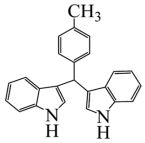
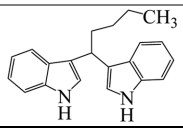
***Scheme* 1.**

***Table* 1.** Optimization of reaction conditions for the synthesis of bis(indolyl)methanes.[a,b]

Entry	Quantity (mole %)	Solvent	Time (minutes)	Yields (%)[c]
1	5	DCM	60	62
2	10	DCM	15	93
3	15	DCM	15	92
4	20	DCM	15	80
5	10	CH_3CN	60	55
6	10	DMF	60	60
7	10	THF	60	65

[a]Reagents: **1** (5 mmol), **2** (2.5 mmol), solvent (10 volume). [b]All reactions were carried out at room temperature condition. [c]Yield refers to isolated product.

***Table* 2.** Synthesis of Bis(indolyl)methanes.[a,b]

Entry	Compound	Time (min)	Yield (%)	Melting Point (°C) Observed/Reported[8,10]
a.		20	95	210-213
b.		15	93	Semisolid
c.		25	92	205-210
d.		20	90	Liquid
e.		15	91	150-155/150-152
f.		15	92	119-120/120-121
g.		20	93	315-318/321-322
h.		25	90	188-190/221-222
i.		20	93	100-101/96-98
j.		25	89	70-72/68-70

[a]Products are characterized by IR, NMR, LCMS and comparison with authentic samples. [b]Isolated yield.

CONCLUSION

In conclusion T3P finds to be an efficient and safe catalyst for the synthesis of bis(indolyl)methanes. The remarkable advantages offered are shortest reaction time, high functional group tolerance, broad applicability and no purification. The method offers excellent alternative for the synthesis of wide variety of bis (indolyl) methanes.

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