

SHORT COMMUNICATION

PCL₅ AS A MILD AND EFFICIENT CATALYST FOR THE SYNTHESIS OF BIS(INDOLYL)METHANES AND DI-BIS(INDOLYL)METHANES

Alireza Hasaninejad^{1*}, Abdolkarim Zare^{2*}, Hashem Sharghi³, Reza Khalifeh³ and Ahmad Reza Moosavi Zare³

¹Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran

²Department of Chemistry, Payame Noor University of Bushehr, Bushehr 1698, Iran

³Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran

(Received December 31, 2007; revised February 4, 2008)

ABSTRACT. Phosphorus pentachloride (PCl₅) can efficiently catalyze the condensation of indoles with aldehydes as well as ketones at room temperature to afford bis(indolyl)methanes and di-bis(indolyl)methanes in high yields and short reaction times.

KEY WORDS: PCl₅, bis(Indolyl)methane, di-bis(Indolyl)methane, Indole, Aldehyde, Ketone

INTRODUCTION

Due to the potent biological activity exhibited by various indole derivatives [1-3], development of indole derivatives synthesis has been of considerable interest in organic synthesis. Among them, bis(indolyl)methanes are the most cruciferous substances for promoting beneficial estrogen metabolism in men and women [4]. They are also effective in the prevention of cancer due to their ability to modulate certain cancer causing estrogen metabolites [5]. Moreover, these compounds may normalize abnormal cell growth associated with cervical dysplasia [6]. The condensation of indoles with carbonyl compounds has been used as an useful route toward bis(indolyl)methanes synthesis [7-25]. Different reagents and catalysts have been applied to achieve this transformation, including AlPW₁₂O₄₀ [7], ZrOCl₂.8H₂O [8], In(OTf)₃ [9], Ln(OTf)₃ [10], Zeokarb-225 [11], LiClO₄ [12], La(PFO)₃ [13], Dy(OTf)₃ [14], surfactant [15,16], CAN [17], PPh₃.HClO₄ [18], ZrCl₄ [19], trichloro-1,3,5-triazine [20], aminosulfonic acid [21], HY-Zeolite [22], silica sulfuric acid [23], silica chloride [24], and P₂O₅/SiO₂ [25]. However, most of the reported methods suffer one or more of the following drawbacks: the necessity of large or stoichiometric amount of reagent, the use of expensive reagents, moderate yields, and long reaction times. Moreover, some methods can not be used for the condensation of indoles with ketones as well as the synthesis of di-bis(indolyl)methanes.

Having the above facts in mind and also in continuation of our previous works on application of phosphorus-containing catalysts in organic synthesis [25-29], we now report here our results on the synthesis of bis(indolyl)methanes via the condensation of indoles with aldehydes and ketones in the presence of catalytic amount of PCl₅ in CH₂Cl₂ at room temperature (Scheme 1).

EXPERIMENTAL

All chemicals were purchased from Merck or Fluka chemical companies. All compounds were identified by comparison of their melting points and/or ¹H NMR data with the authentic

*Corresponding author. E-mail: ahasaninejad@yahoo.com; abdolkarimzare@yahoo.com

samples. Spectra were recorded on the following apparatus: ^1H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm), and mass spectra on a Shimadzu GC MS-QP 1000 EX. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for the condensation of indoles with carbonyl compounds

To a mixture of carbonyl compound (6 mmol), PCl_5 (0.6 mmol) and CH_2Cl_2 (60 mL) in a 100 mL round-bottomed flask was added indole (12 mmol) and the resulting mixture was stirred at room temperature for the appropriate time. Afterward, the reaction mixture was washed with a saturated solution of NaHSO_4 (2 x 50 mL) and NaHCO_3 (2 x 50 mL) and then dried with CaCl_2 . The solvent was evaporated and the crude product was purified by recrystallization from EtOAc/petroleum ether (1/2) or column chromatography on silica gel eluting with EtOAc/petroleum ether (1/2).

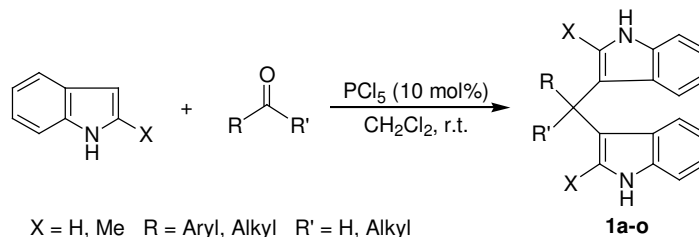
Selected physical and spectral data

3-((1*H*-Indol-3-yl)(phenyl)methyl)-1*H*-indole (**1a**). Pink solid; m.p. 141-143 °C (lit. [17] m.p. 142-144 °C); ^1H NMR (CDCl_3): δ 5.86 (1H, s, ArCH), 6.66 (2H, s), 7.11 (2H, t, $J = 6.9$ Hz), 7.14-7.22 (3H, m), 7.28-7.31 (2H, m), 7.35-7.42 (6H, m), 7.93 (2H, br, NH); ^{13}C NMR (CDCl_3): δ 31.6, 110.9, 111.9, 118.4, 119.5, 121.2, 124.0, 126.3, 127.1, 128.5, 128.6, 137.0, 145.2; MS (m/z): 322 (M^+).

3-((4-(Di(1*H*-indol-3-yl)methyl)phenyl)(1*H*-indol-3-yl)methyl)-1*H*-indole (**2**). Pink solid, m.p. 191 °C (dec.) [lit. [15] m.p. 194 °C (dec.)]; ^1H NMR ($\text{DMSO-}d_6$): δ 5.87 (2H, s, ArCH), 6.54 (4H, s), 7.09-7.18 (8H, m), 7.28-7.41 (12H, m), 8.14 (4H, br, NH); ^{13}C NMR (CDCl_3): δ 30.7, 111.8, 117.9, 118.1, 119.4, 121.1, 124.0, 126.6, 127.9, 137.0, 142.7; MS (m/z): 450 (M^+ - $\text{C}_8\text{H}_6\text{N}$).

RESULTS AND DISCUSSION

At first, we studied the reaction of indole with benzaldehyde (2/1 molar ratio) in order to optimize the reaction conditions with respect to temperature and molar ratio of PCl_5 to the substrate. We found that 10 mol% of PCl_5 was sufficient to produce the desired bis(indolyl)methane **1a** in 95% yield within 25 min in CH_2Cl_2 at room temperature (Scheme 1).



Scheme 1

To choose the appropriate solvent for the reaction, we examined the condensation of indole with benzaldehyde in the presence of PCl_5 in different solvents including CH_2Cl_2 , CHCl_3 , CH_3CN , THF, EtOAc and benzene in which CH_2Cl_2 gave the best results.

In order to emphasize the efficiency of PCl_5 in comparison with the reported reagents, we have tabulated some of the results in Table 1. As it is clear from Table 1, PCl_5 affords the better results.


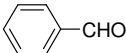

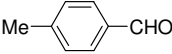

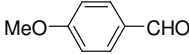
Table 1. Comparative the reaction of indole with benzaldehyde using the reported methods versus our method.

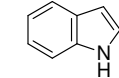

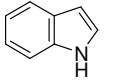
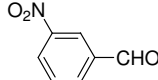
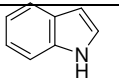
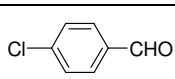
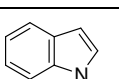
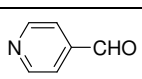
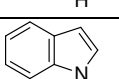
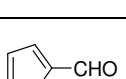
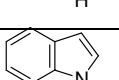
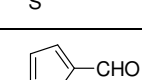
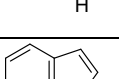
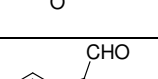
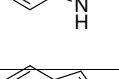
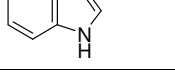
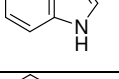
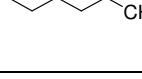
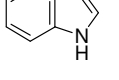
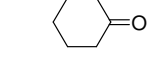
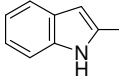
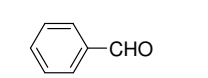
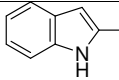
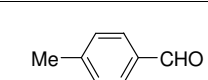
Entry	Reagent and solvent	Time (min)	Yield (%)	Reference
1 ^b	PCl_5 , CH_2Cl_2 , r.t.	25	95	Present method
2	$\text{AlPW}_{12}\text{O}_{40}$, CH_3CN	15	92	[7]
3	$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$, solvent-free	40	84	[8]
4	$\text{In}(\text{OTf})_3/\text{CH}_3\text{CN}$	25	71	[9]
5	$\text{Ln}(\text{OTf})_3/\text{EtOH} \cdot \text{H}_2\text{O}$	720	95	[10]
6	Zeokarb-225/ CH_3CN	450	95	[11]
7	$\text{LiClO}_4/\text{CH}_3\text{CN}$	120	80	[12]
8	$\text{La}(\text{PFO})_3/\text{EtOH}$	30	90	[13]
9	$\text{Dy}(\text{OTf})_3/\text{ionic liquid}$	60	98	[14]

^aIsolated yield.

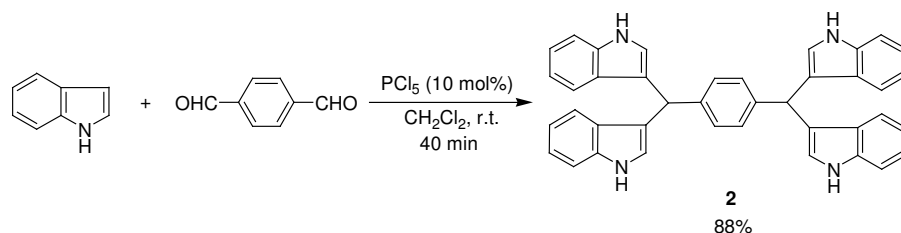
To establish the generality and applicability of this method, indoles were condensed with structurally diverse aldehydes and ketones to furnish bis(indolyl)methanes in high to excellent yields in short reaction times. The results are displayed in Table 2. As Table 2 shows, the presence of both electron-releasing and electron-withdrawing substituents as well as halogens on the aromatic ring of aldehydes had no significant effect upon the yields and the reaction times (Table 2, compounds **1b-f**). However, aliphatic aldehydes and ketones needed longer reaction times and afforded the products in lower yields in comparison with the others (Table 2, compounds **1k** and **1l**). Using 2-methyl-1*H*-indole instead of indole in the reaction slightly decreased the yields and enhanced reaction times (Table 2, compounds **1m-o**). This method can be successfully used for the preparation of di-bis(indolyl)methanes. When indole (4 eq.) was reacted with terephthalaldehyde (1 eq.), di-bis(indolyl methane **2** was obtained in 88% yield after 40 min (Scheme 2).

Table 2. Preparation of bis(indolyl)methanes via the condensation of indoles with carbonyl compounds in the presence of PCl_5 at room temperature.

Indole	Carbonyl compound	Product	Time (min)	Yield ^a (%)	M.p. °C (lit.)
		1a	25	95	141-143 (142-144) [17]
		1b	25	93	94-96 (93-94) [16]
		1c	25	91	186-188 (185-187) [17]

		1d	30	89	217-219 (217-220) [16]
		1e	30	91	222-224 (221-223) [17]
		1f	25	94	78-80 (76-77) [16]
		1g	30	88	161-163 (163-165) [20]
		3h	30	87	146-148 (150-153) [16]
		1i	30	89	315-317 (>300) [16]
		1j	30	89	162 (dec.) [160 (dec.)] [15]
		1k	40	85	70-72 (68-70) [19]
		1l	60	81	163-165 (162-164) [21]
		1m	35	90	244-246 (247-248) [16]
		1n	35	87	175-177 (174-175) [16]
		1o	35	86	242-244 (240-242) [22]

^aIsolated yield.



Scheme 2

In conclusion, we have developed a highly efficient method for the synthesis of bis(indolyl)methanes and di-bis(indolyl)methanes via condensation of indoles with aldehydes as well as ketones. This new strategy offers several advantages including mild reaction conditions, short reaction times, high yields of products, low cost, and simple experimental as well as isolation procedures.

ACKNOWLEDGEMENTS

We appreciate Persian Gulf University, Payame Noor University of Bushehr and Shiraz University Research Councils for financial support of this work. We are also grateful to Prof. A. Khalafi-Nezhad for helpful discussion.

REFERENCES

- Sundberg, R.J. *The Chemistry of Indoles*, Academic Press: New York; **1996**.
- Michnovicz, J.J.; Bradlow, H.L.; Huang, M.J.; Osawa, T.; Ho, C.T.; Rosen, R.T. (Eds.); *Food Phytochemicals for Cancer Prevention I: Fruits and Vegetables*, American Chemical Society: Washington, D.C.; **1994**.
- Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **2003**, 1891.
- Zeligs, M.A. *J. Medicinal Food* **1998**, 67.
- Michnovics, J.J.; Bradlow, H.L. *Food Phytochemicals I: Fruits and Vegetables* **1993**, 282.
- Bell, M.C. *Gynecologic Oncology* **2000**, 78, 123.
- Firouzabadi, H.; Iranpoor, N.; Jafari, A.A. *J. Mol. Catal. A: Chem.* **2006**, 244, 168.
- Firouzabadi, H.; Iranpoor N.; Jafarpour, M. *J. Mol. Catal. A: Chem.* **2006**, 253, 249.
- Nagarajan, R.; Perumal, P.T. *Tetrahedron* **2002**, 58, 1229.
- Chen, D.; Yu, L.; Wang, P.G. *Tetrahedron Lett.* **1996**, 37, 4467.
- Magesh, C.J.; Nagarajan, R.; Karthik, M.; Perumal, P.T. *Applied Catal. A: General* **2004**, 266, 1.
- Yadav, J.S.; Reddy, B.V.S.; Murthy, V.S.R.; Mahesh K.G.; Madan, C. *Synthesis* **2001**, 783.
- Wang, L.; Han, J.H.; Sheng, T.; Fan, J.Z.; Tang, X. *Synlett* **2005**, 337.
- Mi, X.L.; Luo, S.Z.; He, J.Q.; Cheng, J.P. *Tetrahedron Lett.* **2004**, 45, 4567.
- Zolfigol, M.A.; Salehi, P.; Shiri, M.; Tanbakouchian, Z. *Catal. Commun.* **2007**, 173.
- Deb, M.L.; Bhuyan, P.J. *Tetrahedron Lett.* **2006**, 47, 1441.
- Zeng, X.; Ji, S.; Wang, S. *Tetrahedron* **2005**, 61, 10235.
- Nagarajan, R.; Perumal, P.T. *Synth. Commun.* **2002**, 32, 105.
- Nagawade, R.R.; Shinde, D.B. *Bull. Korean Chem. Soc.* **2005**, 26, 1962.
- Sharma, G.V.M.; Reddy, J.J.; Lakshmi, P.S.; Krishna, P.R. *Tetrahedron Lett.* **2004**, 45, 7729.
- Li, J.-T.; Dai, H.-G.; Xu, W.-Z.; Li, T.-S. *Ultrasonics Sonochemistry* **2006**, 24.

22. Reddy, A.V.; Ravinder, K.; Reddy, V.L.N.; Goud, T.V.; Ravikanth, V.; Venkateswarlu, Y. *Synth. Commun.* **2003**, 33, 3687.
23. Pore, D.M.; Desai, U.V.; Thopate, T.S.; Wadgaonkar, P.P. *Arkivoc* **2006**, 12, 75.
24. Hasaninejad, A.; Zare, A.; Sharghi, H.; Shekouhy, M.; Khalifeh, R.; Salimi Beni, A.; Moosavi Zare, A.R. *Can. J. Chem.* **2007**, 85, 416.
25. Hasaninejad, A.; Zare, A.; Sharghi, H.; Niknam, K.; Shekouhy, M. *Arkivoc* **2007**, 14, 39.
26. Hasaninejad, A.; Sharghi, H. *Phosphorus, Sulfur, and Silicon* **2007**, 182, 873.
27. Hasaninejad, A.; Zare, A. *J. Sulfur Chem.* **2007**, 28, 357.
28. Sharghi, H.; Hasaninejad, A. *Phosphorus, Sulfur, and Silicon* **2004**, 179, 2297.
29. Sharghi, H.; Hasaninejad, A. *Helvetica Chim. Acta* **2003**, 86, 408.