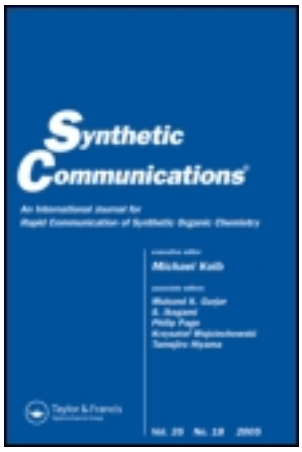


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# ELECTROPHILIC SUBSTITUTION OF INDOLES CATALYZED BY TRIPHENYL PHOSPHONIUM PERCHLORATE: SYNTHESIS OF 3-ACETYL INDOLES AND BIS-INDOLYLMETHANE DERIVATIVES

Rajagopal Nagarajan [a] & Paramasivan T. Perumal

[a] Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai, 600 020, India

Version of record first published: 21 Aug 2006

To cite this article: Rajagopal Nagarajan & Paramasivan T. Perumal (2002): ELECTROPHILIC SUBSTITUTION OF INDOLES CATALYZED BY TRIPHENYL PHOSPHONIUM PERCHLORATE: SYNTHESIS OF 3-ACETYL INDOLES AND BIS-INDOLYLMETHANE DERIVATIVES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:1, 105-109

To link to this article: http://dx.doi.org/10.1081/SCC-120001515

SYNTHETIC COMMUNICATIONS, 32(1), 105–109 (2002)



# ELECTROPHILIC SUBSTITUTION OF INDOLES CATALYZED BY TRIPHENYL PHOSPHONIUM PERCHLORATE: SYNTHESIS OF 3-ACETYL INDOLES AND *BIS*-INDOLYLMETHANE DERIVATIVES

**Rajagopal Nagarajan and Paramasivan T. Perumal***

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai-600 020, India

## ABSTRACT

Triphenyl phosphonium perchlorate (TPP) is found to catalyze the acetylation of indoles with acetic anhydride to give 3-acetyl indoles. Similarly *bis*-indolylmethane derivatives were prepared by the electrophilic substitution reaction of indole with substituted benzaldehydes.

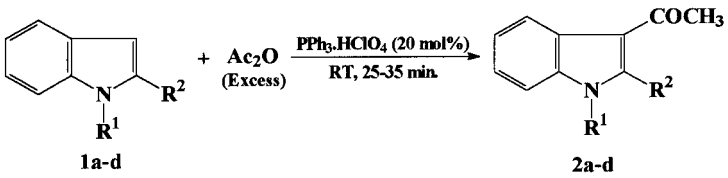
Indole and its derivatives possess a wide range of biological activities and recently the chemistry of indoles was reviewed by Gribble.[1] Acetyl indoles are used as starting material for the synthesis of carbazole,[2] pyrido carbazole[3] and carbolines.[4] Several catalysts like $Si(O_2C{\cdot}CH_2{\cdot}CH_2{\cdot}COOCH_3)_4/SnCl_2$,[5] $HClO_4$ ,[6] $SiCl_4$ [7] and $ZnCl_2$[8] have been used for the acetylation of indoles. However the yields are very low. Okauchi et al.[9]

*Corresponding author. Fax: 91-044-491 1589; E-mail: ptperumal@hotmail.com

reported that the indoles were converted into a metal derivative with $Et_2AlCl$ or $Me_2AlCl$ followed by treatment with acid chlorides to give acetyl indoles.

In this paper we wish to report our observation on acetylation of indoles with triphenyl phosphonium perchlorate (TPP) which is so far not reported in the literature. Recently we have reported that the TPP effectively catalyzing the imino Diels-Alder reaction of imines with electron rich dienophiles to give quinoline derivatives in good yields.[10]

To a stirred solution of indole (**1a**) in excess anhydride, 20 mol% $PPh_3{\cdot}HClO_4$ was added and stirred for 30 min. After work-up, 3-acetyl indole is obtained in 61% yield (Scheme 1). The yields obtained with other indoles are given in Table 1.




*Scheme 1.*

The electrophilic substitution of indoles with carbonyl system produces *bis*-indolylmethanes. *Bis*-indolylmethane derivatives affects central nervous system[11] and also used as tranquilizers.[12]

In the presence of 20 mol% TPP, benzaldehyde **3a** was treated with indole **1a** in acetonitrile and stirred at room temperature for 30 min, the reaction afforded *bis*-indolylmethane **4a** in 66% yield (Scheme 2). The results obtained with other substituted benzaldehydes are given in Table 2.

***Table 1.*** Synthesis of 3-Acetyl Indoles* Catalyzed by 20 mol% $PPh_3{\cdot}HClO_4$

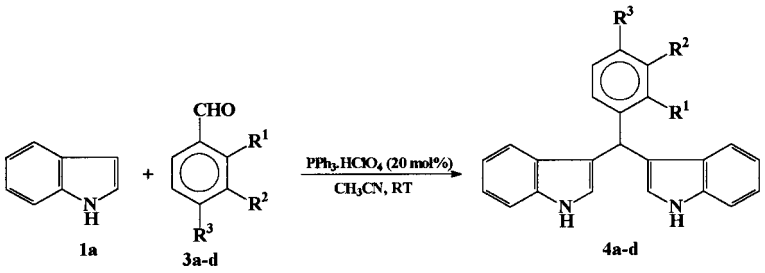
| Sl. No. | Substituents | | Time in min | Yield % |
|---|---|---|---|---|
| | $R^1$ | $R^2$ | | |
| 1 | H | H | 30 | 61 |
| 2 | H | $CH_3$ | 25 | 50 |
| 3 | $SO_2Ph$ | H | 25 | 91 |
| 4 | COPh | H | 30 | 79 |

*The products were characterized by IR, NMR and Mass Spectra.





MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016




*Scheme 2.*

***Table 2.*** Synthesis of *bis*-Indolylmethanes* Catalyzed by 20 mol% $PPh_3 \cdot HClO_4$

| SL. No. | Substituents | | | Time in min | Yield % |
|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | | |
| **1** | H | H | H | 30 | 61 |
| **2** | $NO_2$ | H | H | 25 | 50 |
| **3** | H | H | Cl | 25 | 91 |
| **4** | H | OH | $OCH_3$ | 30 | 79 |

*The products were characterized by IR, NMR and Mass Spectra.

In conclusion, we have shown that TPP effectively catalyzes the acetylation of indoles to 3-acetyl indoles as well as catalyzes the reaction of indole with aromatic aldehydes, leads to *bis*-indolylmethane derivatives. The catalyst is mild and cheap which has an advantage that only 20 mol% required for the reactions.

## TYPICAL EXPERIMENTAL PROCEDURE

### Synthesis of 3-Acetyl Indoles

To a stirred solution of indoles **1a–e** (2.5 mmol) in acetic anhydride (5 mL) protected by guard tube, $PPh_3 \cdot HClO_4$ (0.181 g, 20 mol%) was added and stirred for appropriate time. After the reaction was over, water (50 mL) was added and stirred for 15–25 min. To this solid $NaHCO_3$ was added in portions to aid faster precipitation of acetyl indoles and extracted with $CH_2Cl_2$ ($3 \times 20$ mL). The organic layer was washed with saturated





MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

$NaHCO_3$ (10 mL), brine (10 mL) and dried over anhydrous $Na_2SO_4$, then concentrated under reduced pressure. The residue was purified by column chromatography using silica gel (60–120 mesh) and eluted with petroleum ether–ethyl acetate to afford 3-acetyl indoles. Spectral data for the compound **2c**: $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.32–7.24 (m, 10H), 2.55 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 193.4, 137.4, 134.9, 132.7, 131.5, 129.2, 127.9, 126.5, 125.4, 124.3, 123.7, 122.6, 121.8, 113.5, 112.6, 27.9; MS *m*/*z* 299 ($M^+$); IR (KBr): 1671, 1378, 1170 $cm^{-1}$.

### Synthesis of *bis*-Indolylmethanes

To a stirred solution of benzaldehyde (1 mmol) and indole **1a** (0.234 g, 2.0 mmol) in acetonitrile (10 mL) protected by guard tube TPP (0.091 g, 20 mol%) was added and stirred for appropriate time. To the reaction mixture water (10 mL) was added and extracted with chloroform (3 × 10 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$, and then concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60–120 mesh) and eluted with petroleum ether–ethyl acetate to afford 3,3′-*bis*-indolylphenylmethane **4a** in 66% yield.$^1$H NMR ($CDCl_3$, 300 MHz): δ 7.59–7.02 (m, 15H), 6.50 (s, 2H), 5.90 (s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 143.9, 136.4, 128.6, 128.1, 126.9, 126.0, 123.5, 121.7, 119.8, 119.4, 119.1, 111.0, 40.0; MS *m*/*z* 322 ($M^+$); IR (KBr): 3394, 3051, 455, 747 $cm^{-1}$.

## REFERENCES

1. Gribble, G.W. J. Chem. Soc., Perkin Trans 1 **2000**, 1045.
2. Jeevanandam, A.; Srinivasan, P.C. J. Chem. Soc. Perkin Trans 1 **1995**, 2663.
3. (a) Gribble, G.W.; Keavy, D.J.; Davis, D.A.; Saulnier, M.G.; Pelcman, B.; Barden, T.C.; Sibi, M.P.; Olson, E.R.; Belbruno, J.J. J. Org. Chem. **1992**, *57*, 5878. (b) Gribble, G.W.; Saulnier, M.G.; Sibi, M.P.; Obaza-Nutiatits, J.A. J. Org. Chem. **1984**, *49*, 4518.
4. Markgraf, J.H.; Synder, S.A.; Vosburg, D.A. Tetrahedron **2000**, *56*, 5329.
5. Kost, A.N.; Mitropal'skaya, V.N.; Pornova, S.L.; Krasnova, V.A. J. Gen. Chem. USSR (English Transl) **1964**, *34*, 3025.
6. Dorofeenko, G.N. Zh. Veses, Khim. Obshehestva im. D.I. Mendeleeva, **1960**, *5*, 354. Chem. Abstr. **1960**, *54*, 22563.





Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

7. Yur'er, Y.K.; Elyakov, G.B. Zh. Obshch. Kim. **1956**, *26*, 2350. Chem. Abstr. **1957**, *51*, 5042.
8. Douglas, B.; Krikpatrick, J.L.; Moore, B.P.; Weisbach, J.A. Australian J. Chem. **1964**, *17*, 246.
9. Okauchi, T.; Honaga, M.; Minami, T.; Owa, T.; Kiloh, K.; Yoshino, H. Org. Lett. **2000**, 1485.
10. Nagarajan, R.; Chitra, S.; Perumal, P.T. Tetrahedron **2001** (Accepted for publication).
11. Foldeak, S.; Czombas, J.; Matkovics, B. Acta. Univ. Szeged. Acta Phys. Chem. **1965**, *11*, 115.
12. Porszasz, J.; Katalin, G.P.; Foleak, S.; Malkovics, B. Acta. Physical. Acad. Sci. Hunt, **1996**, *29*, 299.

Received in the Netherlands February 28, 2001