This article was downloaded by: [North Carolina State University] On: 27 August 2012, At: 00:17 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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

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

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

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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 3acetyl 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 carbazole³ and carbolines.⁴ Several catalysts like Si(O₂C·CH₂·CH₂· COOCH₃)₄/SnCl₂,⁵ HClO₄, ⁶ SiCl₄ ⁷ and ZnCl₂⁸ have been used for the acetylation of indoles. However the yields are very low. Okauchi et al.⁹

Copyright © 2002 by Marcel Dekker, Inc.

www.dekker.com

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

ORDER		REPRINTS
-------	--	----------

NAGARAJAN AND PERUMAL

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% PPh₃·HClO₄ 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.





The electrophilic substitution of indoles with carbonyl system produces *bis*-indolylmethanes. *Bis*-indolylmethane derivatives affects central nervous system¹¹ and also used as tranquilizers.¹²

In the presence of $20 \mod\%$ 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.

	Substituents		Time in	Viald
Sl. No.	R ¹	\mathbb{R}^2	min	%
1	Н	Н	30	61
2	Н	CH ₃	25	50
3	SO_2Ph	Н	25	91
4	COPh	Н	30	79

Table 1.	Synthesis of (3-Acetyl Indoles*	Catalyzed by	$\sqrt{20 \text{ mol}\%}$	PPh ₃ ·HClO ₄
					.,

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

Marcel Dekker, Inc.

270 Madison Avenue, New York, New York 10016

106

ORDER		REPRINTS
-------	--	----------

ELECTROPHILIC SUBSTITUTION OF INDOLES



Table 2. Synthesis of bis-Indolylmethanes* Catalyzed by 20 mol% PPh₃·HClO₄

	Substituents		Time in	Vield	
SL. No.	\mathbf{R}^1	\mathbb{R}^2	R ³	min	%
1	Н	Н	Н	30	61
2	NO_2	Н	Н	25	50
3	Н	Н	Cl	25	91
4	Н	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, PPh₃·HClO₄ (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 NaHCO₃ was added in portions to aid faster precipitation of acetyl indoles and extracted with CH₂Cl₂ (3 × 20 mL). The organic layer was washed with saturated



Marcel Dekker, Inc.

270 Madison Avenue, New York, New York 10016

ORDER		REPRINTS
-------	--	----------

NAGARAJAN AND PERUMAL

NaHCO₃ (10 mL), brine (10 mL) and dried over anhydrous Na₂SO₄, 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**: ¹H NMR (CDCl₃, 300 MHz): δ 8.32–7.24 (m, 10H), 2.55 (s, 3H); ¹³C NMR (CDCl₃, 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 Na₂SO₄, 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.¹H NMR (CDCl₃, 300 MHz): δ 7.59–7.02 (m, 15H), 6.50 (s, 2H), 5.90 (s, 1H); ¹³C NMR (CDCl₃, 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.
- (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.
- Dorofeenko, G.N. Zh. Veses, Khim. Obshehestva im. D.I. Mendeleeva, 1960, 5, 354. Chem. Abstr. 1960, 54, 22563.

Copyright © Marcel Dekker, Inc. All rights reserved

ORDER		REPRINTS
-------	--	----------

ELECTROPHILIC SUBSTITUTION OF INDOLES

- 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.
- 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

Downloaded by [North Carolina State University] at 00:17 27 August 2012



109

Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the <u>U.S. Copyright Office</u> for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on <u>Fair Use in the Classroom</u>.

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our <u>Website</u> User Agreement for more details.

Order now!

Reprints of this article can also be ordered at http://www.dekker.com/servlet/product/DOI/101081SCC120001515