

NH₄Cl-promoted synthesis of symmetrical and unsymmetrical triindolymethanes under solvent-free conditions

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The synthesis of various triindolymethanes from indole-3-carboxaldehyde, using indole derivatives as reactants and NH₄Cl as catalyst under solvent-free conditions, is described. This methodology provides access to both symmetrical and unsymmetrical triindolymethanes in excellent yields. With *N*-methylindole particularly, indole-3-carboxaldehyde appears to act as a formyl donor, leading to the exclusive formation of a symmetrically trisubstituted product. The novelty of the methodology lies in its operational simplicity, environment friendly reaction conditions, and inexpensive and easy availability of the catalyst. A plausible mechanism of formation of the products is suggested.

Keywords: triindolymethanes, ammonium chloride, solvent free synthesis

Triindolymethane (TRIM) has received considerable attention due to its various biological activities^{1,2} and industrial importance.³ It can be used as acceptor of hydride ions⁴ and it also acts as an effective chloride ion receptor.⁵ Despite their importance from the pharmacological, industrial and synthetic points of view, comparatively few methods have been developed for the preparation of triindolymethanes. The formation of triindolymethane from indole and ethyl orthoformate in the presence of ethanolic HCl first appeared in the literature in 1952.⁶ Bergman⁷ has reported the synthesis of TRIMs by using substituted indoles and acetic formic anhydride. The preparation of symmetrical TRIMs by the condensation of indoles with orthoformate in presence of *p*-TSA was reported by Akgün *et al.*⁸ Chakraborty and coworkers⁹ have proposed a useful variation of this reaction using acid-washed montmorillonite clay as catalyst. Other synthetic methods have appeared in the literature.^{10,11} Recently, we reported the synthesis of TRIMs using different Lewis acids and also molecular iodine as catalyst.¹² Despite the availability of different methodologies, there is scope for the development of a clean and efficient process with newer reagents, as one of the recent challenges in organic synthesis is the demand for new methodologies that afford products of structural complexity in fewer synthetic steps and from simple starting materials.

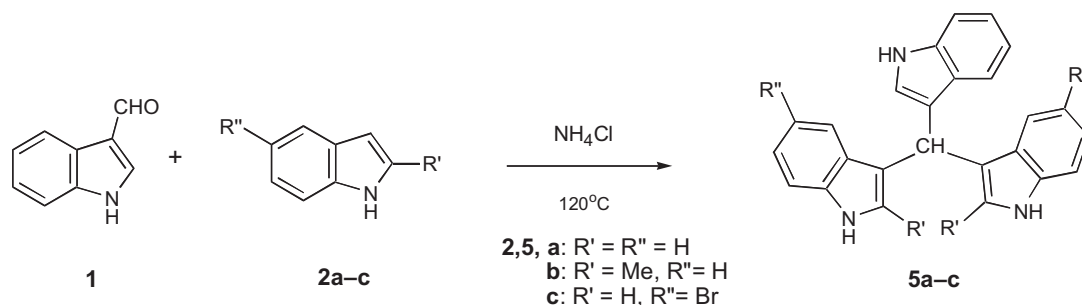
Progress in the field of solvent-free reactions is gaining much importance from both an environmental and an economic point of view, because solvent-free processes not only reduce the use of potentially hazardous organic solvents, but also minimise the formation of side products. Herein we report the solvent-free synthesis of triindolymethanes using ammonium chloride as catalyst with better yields than hitherto.

Ammonium chloride (NH₄Cl) is a cheap, eco-friendly and easily available substance, which is used in various organic

synthetic processes such as aliphatic Claisen rearrangements,¹³ the Biginelli synthesis of 3,4-dihydropyrimidinones,¹⁴ in Ugi four-component reactions,¹⁵ and also in a four-component synthesis of pyrrolo[3,4-*b*]pyridinones.¹⁶ It is used in the reduction of nitrophenols;^{17,18} the reduction of alkyl and acyl azides to the corresponding amines and amides was also achieved using Zn and NH₄Cl.¹⁹ Azizian *et al.* claimed the NH₄Cl-catalysed one-pot synthesis of diindolymethanes (DIM) under solvent free conditions.²⁰ But to the best of our knowledge there appears to have been no report of the synthesis of triindolymethanes (TRIMs) using NH₄Cl as catalyst under solvent-free conditions.

Results and discussion

As with our previous work on the synthesis of triindolymethane, we utilised indole-3-carboxaldehyde (**1**) as substrate, indole (**2a**) as reactant and NH₄Cl as catalyst in the initial study. The reactions were carried out without solvent in a reaction flask. Thus, the reaction with **1** and **2a** using NH₄Cl at elevated temperature (120 °C) under solvent-free conditions yielded **5a** as the only isolable product (Scheme 1). The characterisation of **5a** was accomplished by spectral analysis (¹H, ¹³C NMR, MS) and was confirmed as a symmetrical triindolymethane.¹² The same reaction was repeated varying the reaction time and proportion of the catalyst to optimise the yield of the product. It was observed that for **5a**, the mole ratio with 1: 2: 1 of indole-3-carboxaldehyde, indole and NH₄Cl at 120 °C provided a maximum yield within 30 min. When similar reactions were performed with substituted indoles (**2b**, **2c**, **3** and **4**) as reactants, some variations were observed in the yield of the products and also in reaction time with respect to **5a** (Table 1).



Scheme 1 NH₄Cl catalysed reaction of indole-3-carboxaldehyde (**1**) with indoles **2a-c**.

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Table 1 Synthesis of TRIMs from **1** and indoles **2–4** using NH_4Cl as catalyst under solvent free conditions

Indole	Product/s	Time/h	Catalyst/mmol	Yield(s)/%
2a	5a	0.5	0.5	74
2a	5a	0.5	1	96
2a	5a	1.5	2	96
2b	5b	1	0.5	57
2b	5b	2	1	87
2b	5b	4	2	87
2c	5c	1	0.5	74
2c	5c	1.5	1	96
2c	5c	3	1	96
3	6 + 2a	1	0.5	30 + 10
3	6 + 2a	3	1	45 + 25
3	6 + 2a	5	2	45 + 25
4	7a + 7b + 2a	1	0.5	15 + 35 + 5
4	7a + 7b + 2a	3	1	20 + 55 + 10
4	7a + 7b + 2a	5	1	20 + 55 + 10

^aAll the reactions were performed at 120 °C; increase of temperature did not improve the yields.

^bAll the products were characterised by IR, NMR and mass spectrometry.

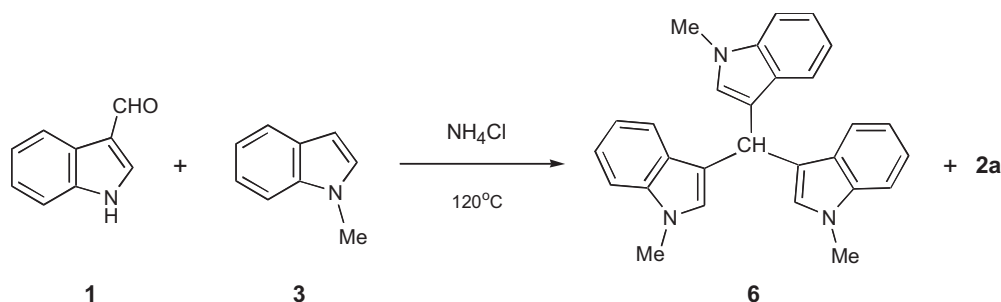
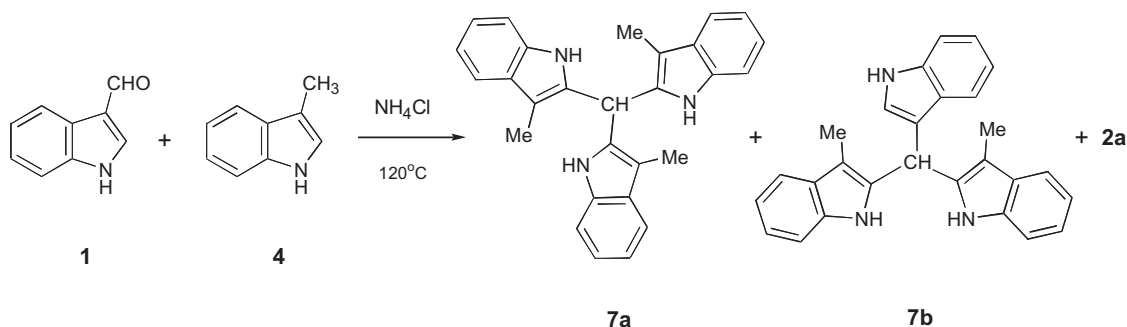
^cYield of isolated pure products.

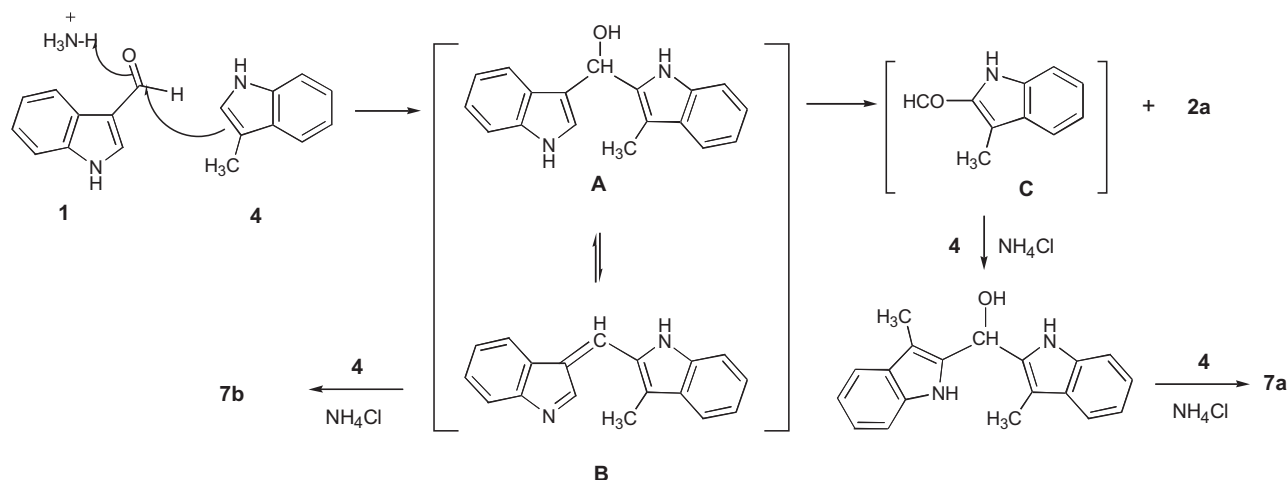
Thus, from the reactions of **2b** (2-methylindole) and **2c** (5-bromoindole) with **1**, only the unsymmetrical products **5b** and **5c**, respectively, were obtained. On the other hand, the reaction using *N*-methylindole (**3**) as reactant yielded only the symmetrical product **6**,⁹ along with indole (**2a**) (Scheme 2). However, when 3-methylindole (**4**) was the reactant the formation of the products took a different turn; the reaction yielded both the symmetrical (**7a**) and unsymmetrical (**7b**) triindolymethanes, along with **2a**²¹ (Scheme 3). The yield of the unsymmetrical product was appreciably higher than that of the symmetrical product.

A plausible mechanism for the formation of symmetrical and unsymmetrical TRIMs (**7a** and **7b**), using NH_4Cl as the catalyst, is depicted in Scheme 4. It is presumed that in the reaction NH_4Cl may enhance the electrophilic character of the carbonyl carbon of **1** by hydrogen bonding,²⁰ facilitating the nucleophilic attack of 3-methylindole (**4**) and thus resulted in formation of the intermediate **A**, in equilibrium with intermediate **B**. NH_4Cl again might activate the intermediate **B** to promote a Michael-type addition of 3-

methylindole (**4**) and finally facilitate the formation of the unsymmetrical triindolymethane **7b**. On the other hand the formation of symmetrical TRIM (**7a**) may take place through the intermediate **A**, where *in situ* loss of indole (**2a**) resulted the intermediate aldehyde **C**.^{22,23} Two moles of **4** then react with **C**, culminating in **7a**. The formation of **2a** in this reaction indicated that there must be a mechanism for the passing of the CHO group from **1** to **4** through the intermediate **A**. We believe that the mechanism for the formation of **6** follows the same pathway as described for **7a**. However, the formation of an unsymmetrical triindolymethane from the reactions of **3** could not be detected even after several attempts.

We attempted similar reactions using indole-2-carboxylic acid, indole-3-acetic acid, 3-indolylacetonitrile, 1-methylindole-3-acetic acid, and indole-3-carboxylic acid as the reactants. In these cases, we were unable to isolate any products from the reactions even after a longer reaction time (10 h) and also using higher amounts of catalyst (10 mmol). We presume that the nucleophilicity of indole, which is highly

**Scheme 2** NH_4Cl catalysed reaction of indole-3-carboxaldehyde with *N*-methylindole.**Scheme 3** NH_4Cl catalysed reaction of indole-3-carboxaldehyde with 3-methylindole.



Scheme 4 Route to the symmetrical and unsymmetrical triindolymethanes **7a** and **7b**.

reduced by the electron withdrawing groups at the 2 or 3 positions, plays a vital role in the reactions.

In summary, we have developed a simple, efficient, and environmentally acceptable synthetic method for the preparation of triindolymethanes using NH_4Cl as catalyst under solvent free conditions. The mild reaction conditions, ease of product separation, ready availability of the catalyst, and excellent yields of products, makes this procedure an acceptable one for the synthesis of triindolymethanes. The formation of products by apparent migration of the formyl group from one indole nucleus to another is an interesting sideline of these reactions.

Experimental

IR spectra were recorded in KBr pellets on a JASCO FTIR (model 410) instrument. ^1H and ^{13}C NMR spectra were recorded in pyridine- d_5 or $\text{DMSO}-d_6$ with tetramethylsilane as internal standard on a Bruker 300 MHz DPX spectrometer operating at 300 and 74.99 MHz respectively. ESI-MS (positive-ion) was recorded using LC-ESI-Q-TOF micro mass spectrometer. Indole-3-carboxaldehyde and other indole derivatives were purchased from Aldrich Chemicals Ltd (USA). Organic solvents for chromatographic purification were purchased from E. Merck (India) and were of analytical grade. All chromatographic purifications were performed with silica gel (100–200 mesh) obtained from SRL (India).

Triindolymethane synthesis using NH_4Cl : general procedure

A mixture of indole-3-carboxaldehyde (**1**, 0.145 g, 1 mmol), indole (**2–4**, 2 mmol) and NH_4Cl (0.055 g, 1 mmol) in a conical flask was heated in an oil bath with occasional stirring with a glass rod at 120°C for the appropriate time (see Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and cold water was added to dissolve NH_4Cl . The product was filtered off and the residue was purified by column chromatography, eluting with petroleum ether/ethyl acetate.

Tri-(3-indolyl)methane (5a): Colourless prisms, m.p. 241°C (acetone–pet. ether) (lit.²⁴ $245\text{--}247^\circ\text{C}$). IR: 3386, 1624, 1428 cm^{-1} . NMR ($\text{DMSO}-d_6$): δ_{H} 6.11 (s, 1H, Ar_3CH), 6.88 (t, 3H, $J = 7.2\text{ Hz}$), 6.98 (s, 3H), 7.04 (t, 3H, $J = 7.2\text{ Hz}$), 7.37 (d, 3H, $J = 7.8\text{ Hz}$), 7.44 (d, 3H, $J = 7.8\text{ Hz}$), 10.74 (s, 3H, NH); δ_{C} 31.0 (Ar_3CH), 111.4 (CH), 118.0 (CH), 118.3 (C), 119.3 (CH), 120.7 (CH), 123.2 (CH), 126.8 (C), 136.6 (C). ESI-MS: m/z 362 $[\text{M} + \text{H}]^+$.

(3-Indolyl)-bis-(2-methylindol-3-yl)methane (5b): Colourless needles, m.p. $260\text{--}262^\circ\text{C}$ (acetone–pet. ether) (lit.¹² $260\text{--}262^\circ\text{C}$). IR: 3397, 1458, 1343, 1297 cm^{-1} . NMR ($\text{DMSO}-d_6$): δ_{H} 2.09 (s, 6H, CH_3), 6.07 (s, Ar_3CH), 6.14 (s, 1H), 6.67 (m, 2H), 6.84 (m, 5H), 7.06 (m, 2H), 7.22 (m, 2H), 7.37 (d, $J = 7.8\text{ Hz}$, 1H), 10.65 and 10.70 (m, 3H, NH); δ_{C} 12.8 (CH_3), 31.1 (Ar_3CH), 111.1 (CH), 112.2 (CH), 113.2 (C), 113.5 (C), 118.6 (CH), 118.7 (CH), 118.9 (CH), 119.1 (CH), 119.3 (CH), 119.8 (CH), 120.2 (CH), 121.7 (CH), 124.2 (CH), 128. (C), 129.3 (C), 129.7 (C), 132.2 (C), 132.6 (C), 135.8 (C), 135.9 (C), 137.5 (C). ESI-MS: m/z 390 $[\text{M} + \text{H}]^+$.

Bis-(5-bromoindol-3-yl)-(3-indolyl)methane (5c): Colourless needles, m.p. $239\text{--}241^\circ\text{C}$ (acetone–pet. ether) (lit.¹² $238\text{--}240^\circ\text{C}$). IR: 3420, 1451, $1336, 1213\text{ cm}^{-1}$. NMR ($\text{DMSO}-d_6$): δ_{H} 6.07 (s, 1H, Ar_3CH), 6.88 (m, 1H), 6.96 (s, 1H), 7.02 (bs, 3H), 7.15 (m, 2H), 7.34 (m, 4H), 7.53 (bs, 2H), 10.79 (1H, NH-indole), 11.01 (2H, NH-5-bromoindole); δ_{C} 30.5 (Ar_3CH), 110.7 (C), 110.8 (C), 111.5 (CH), 113.5 (CH), 113.6 (CH), 117.4 (C), 117.6 (C), 117.7 (C), 118.1 (CH), 119.3 (CH), 120.7 (CH), 120.8 (CH), 121.4 (CH), 123.2 (CH), 123.3 (CH), 125.0 (CH), 126.6 (C), 126.7 (C), 128.4 (C), 128.5 (C), 135.3 (C), 136.6 (C). ESI-MS: m/z 542 $[\text{M} + \text{Na}]^+$.

Tris-(1-methylindol-3-yl)methane (6): Orange needles, m.p. $255\text{--}256^\circ\text{C}$ (acetone–pet. ether) (lit.⁹ $256\text{--}258^\circ\text{C}$). IR: 1612, 1471, 1331 cm^{-1} . NMR ($\text{Py}-d_5$): δ_{H} 3.40 (s, 9H, CH_3), 6.52 (s, 1H, Ar_3CH), 6.94 (s, 3H, CH), 7.10 (t, 3H, $J = 7.2\text{ Hz}$, CH), 7.26 (t, 3H, $J = 7.8\text{ Hz}$, CH), 7.35 (d, 3H, $J = 8.1\text{ Hz}$, CH), 7.77 (d, 3H, $J = 8.1\text{ Hz}$, CH). ESI-MS: m/z 404 $[\text{M} + \text{H}]^+$.

Tris-(3-methylindol-2-yl)methane (7a): Colourless prisms, m.p. $318\text{--}320^\circ\text{C}$ (acetone–pet. ether) (lit.⁹ $319\text{--}320^\circ\text{C}$). IR: 3383, 1624, 1429 cm^{-1} . NMR ($\text{Py}-d_5$): δ_{H} 2.13 (s, 9H, CH_3), 6.29 (s, 1H, Ar_3CH), 7.04 (m, 6H), 7.37 (d, 3H, $J = 7.8\text{ Hz}$), 7.48 (d, 3H, $J = 7.8\text{ Hz}$), 10.50 (s, 3H, NH); δ_{C} 9.1 (CH_3), 34.6 (Ar_3CH), 107.4 (C), 112.1 (CH), 118.7 (CH), 119.1 (CH), 121.5 (CH), 129.6 (C), 133.9 (C), 136.4 (C). ESI-MS: m/z 404 $[\text{M} + \text{H}]^+$.

(3-Indolyl)-bis-(3-methylindol-2-yl)methane (7b): Colourless needles, m.p. $229\text{--}230^\circ\text{C}$ (acetone–pet. ether) (lit.¹² $228\text{--}230^\circ\text{C}$). IR: 3404, 1623, 1454 cm^{-1} . NMR ($\text{Py}-d_5$): δ_{H} 2.44 (s, 6H, CH_3), 5.09 (s, 1H, Ar_3CH), 6.69 (s, 1H), 7.03 (t, 1H, $J = 6\text{ Hz}$), 7.21 (m, 4H), 7.31 (d, 2H, $J = 7.8\text{ Hz}$), 7.42 (d, 1H, $J = 8.1\text{ Hz}$), 7.61 (d, 1H, $J = 7.8\text{ Hz}$), 7.73 (d, 2H, $J = 6\text{ Hz}$), 11.27 (s, 2H, NH-3-Me-Indole), 11.86 (s, 1H, NH-Indole); δ_{C} 9.1 (CH_3), 34.1 (Ar_3CH), 107.2 (C), 111.7 (CH), 112.2 (CH), 115.6 (C), 118.8 (CH), 119.2 (CH), 119.7 (CH), 121.3 (CH), 122.1 (CH), 125.2 (CH), 128.1 (C), 130.4 (C), 136.5 (C), 136.9 (C), 138.2 (C). ESI-MS: m/z 390 $[\text{M} + \text{H}]^+$.

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References

- R.J. Sundberg, *The chemistry of indoles*, Academic Press, New York, 1996.
- J. Li, L. Wang, B. Li and G. Zhang, *Heterocycles*, 2003, **60**, 1307.
- R. Muthyala, A.R. Katritzky and X. Lan, *Dyes Pigments*, 1994, **25**, 303.
- M.N. Preobrazhenskaya, A.M. Korolev, I.I. Rozhkov, L.N. Yudina, E.I. Lazhko, E. Aiello, A.M. Almerico and F. Mingoa, *Il Farmaco*, 1999, **54**, 265.
- W. Oi, M. Nisiki and K. Ito, *Lett. Org. Chem.*, 2007, **4**, 112.

- 6 J. Harley-Mason and J.D. Bu'lock, *Biochem. J.*, 1952, **51**, 430.
- 7 J. Bergman, *J. Heterocycl. Chem.*, 1971, **8**, 329.
- 8 E. Akgün, U. Pindur and J. Müller, *J. Heterocycl. Chem.*, 1983, **20**, 1303.
- 9 M. Chakrabarty, S. Sarkar, A. Linden and B.K. Stein, *Synth. Commun.*, 2004, **34**, 1801.
- 10 T. Kurihara, T. Iani, H. Imai and K. Nasu, *Chem. Pharm. Bull.*, 1980, **28**, 2972.
- 11 S.B. Mahato, S. Garai, M. Weber and P. Luger, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2767.
- 12 A. Hazra, P. Paira, K.B. Sahu, S. Banerjee and N.B. Mondal, *Catalysis Commun.*, 2008, **9**, 1681.
- 13 J.W. Ralls, R.E. Lundin and G.F. Bailley, *J. Org. Chem.*, 1963, **28**, 3521.
- 14 A. Shaabani, A. Bazgir and F. Teimouri, *Tetrahedron Lett.*, 2003, **44**, 857.
- 15 D. Bonne, M. Dekhane and Z. Zhu, *Org. Lett.*, 2004, **6**, 4771.
- 16 P. Janvier, X. Sun, H. Bienayme and Z. Zhu, *J. Am. Chem. Soc.*, 2003, **124**, 2560.
- 17 V. Sridharan, M. Karpagavalli, S. Muthusubramanian and S. Sivasubramanian, *Indian J. Chem. B*, 2004, **43**, 2243.
- 18 M.K. Basu, F.F. Becker and B.K. Banik, *Tetrahedron Lett.*, 2000, **41**, 5603.
- 19 W. Lin, X. Zhang, Z. He, L. Gong and A. Mi, *Synth. Commun.*, 2002, **32**, 3279.
- 20 J. Azizian, F. Teimouri and M.R. Mohammadizadeh, *Catalysis Commun.*, 2007, **8**, 1117.
- 21 M. Chakrabarty and S. Sarkar, *Tetrahedron Lett.*, 2002, **43**, 1351.
- 22 E. Leete, *J. Am. Chem. Soc.*, 1959, **81**, 6023.
- 23 L.J. Dolby and G.W. Gribble, *Tetrahedron*, 1968, **24**, 6377.
- 24 Z.H. Zhang and J. Lin, *Synth. Commun.*, 2007, **37**, 209.