NH_4Cl-promoted synthesis of symmetrical and unsymmetrical triindolylmethanes under solvent-free conditions

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The synthesis of various triindolylmethanes from indole-3-carboxaldehyde, using indole derivatives as reactants and NH_4Cl as catalyst under solvent-free conditions, is described. This methodology provides access to both symmetrical and unsymmetrical triindolylmethanes 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: triindolylmethanes, ammonium chloride, solvent free synthesis

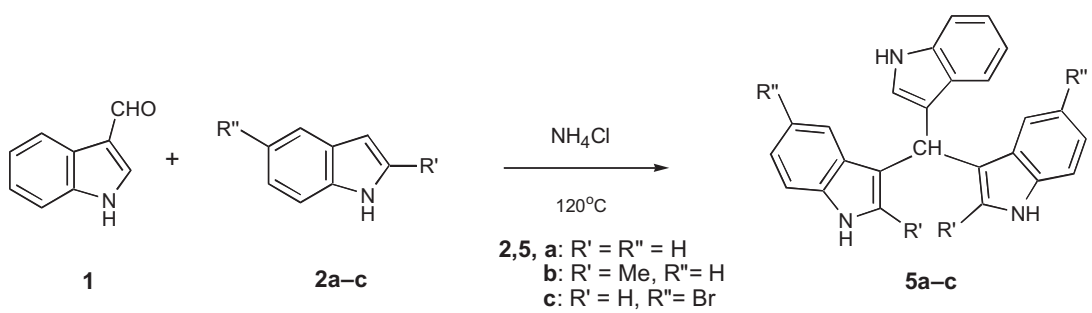
Triindolylmethane (TRIM) has received considerable attention due to its various biological activities[1,2] and industrial importance.[3] It can be used as acceptor of hydride ions[4] and it also acts as an effective chloride ion receptor.[5] Despite their importance from the pharmacological, industrial and synthetic points of view, comparatively few methods have been developed for the preparation of triindolylmethanes. The formation of triindolylmethane from indole and ethyl orthoformate in the presence of ethanolic HCl first appeared in the literature in 1952.[6] Bergman[7] 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 coworkers[9] 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 triindolylmethanes using ammonium chloride as catalyst with better yields than hitherto.

Ammonium chloride (NH_4Cl) 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 NH_4Cl.[19] Azizian *et al.* claimed the NH_4Cl-catalysed one-pot synthesis of diindolylmethanes (DIM) under solvent free conditions.[20] But to the best of our knowledge there appears to have been no report of the synthesis of triindolylmethanes (TRIMs) using NH_4Cl as catalyst under solvent-free conditions.

Results and discussion

As with our previous work on the synthesis of triindolylmethane, we utilised indole-3-carboxaldehyde (**1**) as substrate, indole (**2a**) as reactant and NH_4Cl 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 NH_4Cl 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, ^{13}C NMR, MS) and was confirmed as a symmetrical triindolylmethane.[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 NH_4Cl 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** (Table1).



Scheme 1 NH_4Cl 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

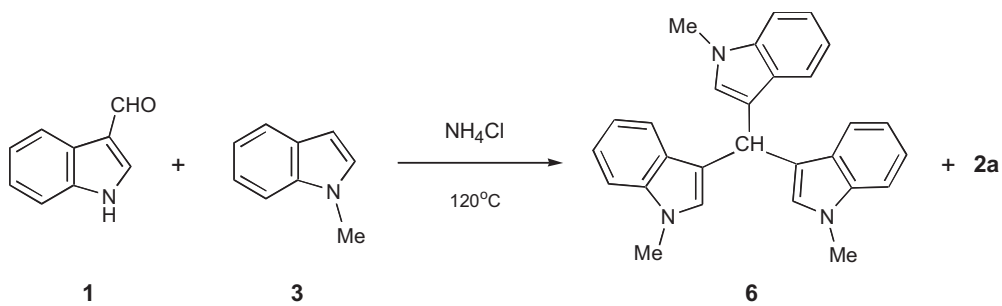
Indole	Product/s	Time/h	Catalyst/mmol	Yield(s)/%
2a	**5a**	0.5	0.5	74
2a	**5a**	0.5	1	96
2a	**5a**	1.5	2	96
2b	**5b**	1	0.5	57
2b	**5b**	2	1	87
2b	**5b**	4	2	87
2c	**5c**	1	0.5	74
2c	**5c**	1.5	1	96
2c	**5c**	3	1	96
3	**6 + 2a**	1	0.5	30 + 10
3	**6 + 2a**	3	1	45 + 25
3	**6 + 2a**	5	2	45 + 25
4	**7a +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

[a]All the reactions were performed at 120 °C; increase of temperature did not improve the yields.
[b]All the products were characterised by IR, NMR and mass spectrometry.
[c]Yield of isolated pure products.

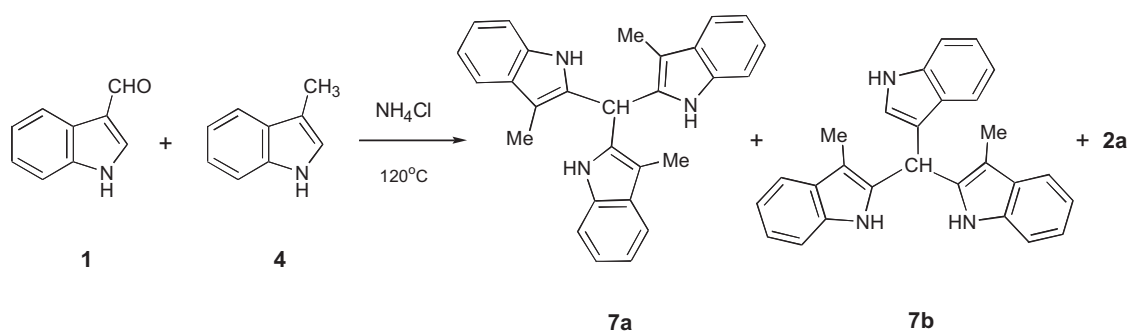
Thus, from the reactions of **2b** (2-methylindole) and **2c** (5-bromoindole) with **1**, only the unsymmetrical products **5b** and **5c**, respectively, were obtained. On the other hand, the reaction using *N*-methylindole (**3**) as reactant yielded only the symmetrical product **6**,[9] along with 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**) triindolylmethanes, 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 triindolylmethane **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 triindolylmethane from the reactions of **3** could not be detected even after several attempts.

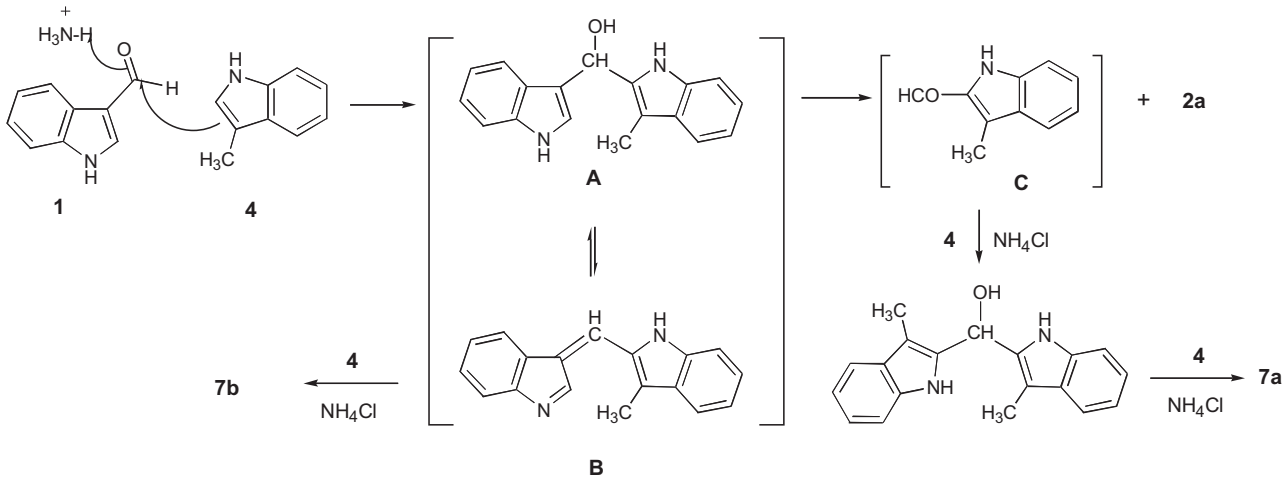
We attempted similar reactions using indole-2-carboxylic acid, indole-3-acetic acid, 3-indolylacetonitrile, 1-methylindole-3-acetic acid, and indole-3-carboxylic acid as the reactants. In these cases, we were unable to isolate any products from the reactions even after a longer reaction time (10 h) and 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 triindolylmethanes **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 triindolylmethanes 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 triindolylmethanes. 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 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).

Triindolylmethane 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] 245–247 °C). IR: 3386, 1624, 1428 cm^{-1}. NMR (DMSO-d_6): δ_H δ 6.11 (s, 1H, Ar_3CH), 6.88 (t, 3H, J = 7.2 Hz), 6.98 (s, 3H), 7.04 (t, 3H, J = 7.2 Hz), 7.37 (d, 3H, J = 7.8 Hz), 7.44 (d, 3H, J = 7.8 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 $[M + H]^+$.

(3-Indolyl)-bis-(2-methylindol-3-yl)methane (**5b**): Colourless needles, m.p. 260–262 °C (acetone–pet. ether) (lit.[12] 260–262 °C). IR: 3397, 1458, 1343, 1297 cm^{-1}. NMR (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 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 $[M + H]^+$.

Bis-(5-bromoindol-3-yl)-(3-indolyl)methane (**5c**): Colourless needles, m.p. 239–241 °C (acetone–pet. ether) (lit.[12] 238–240 °C). IR: 3420, 1451, 1336, 1213 cm^{-1}. NMR (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 $[M + Na]^+$.

Tris-(1-methylindol-3-yl)methane (**6**): Orange needles, m.p. 255–256 °C (acetone–pet.ether)(lit.[9] 256–258 °C). IR: 1612, 1471, 1331 cm^{-1}. NMR (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 Hz, CH), 7.26 (t, 3H, J = 7.8 Hz, CH), 7.35 (d, 3H, J = 8.1 Hz, CH), 7.77 (d, 3H, J = 8.1 Hz, CH). ESI-MS: *m/z* 404 $[M + H]^+$.

Tris-(3-methylindol-2-yl)methane (**7a**): Colourless prisms, m.p. 318–320 °C (acetone–pet. ether) (lit.[9] 319–320 °C). IR: 3383, 1624, 1429 cm^{-1}. NMR (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 Hz), 7.48 (d, 3H, J = 7.8 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 $[M + H]^+$.

(3-Indolyl)-bis-(3-methylindol-2-yl)methane (**7b**): Colourless needles, m.p. 229–230 °C (acetone–pet. ether) (lit.[12] 228–230 °C). IR: 3404, 1623, 1454 cm^{-1}. NMR (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 Hz), 7.21 (m, 4H), 7.31 (d, 2H, J = 7.8 Hz), 7.42 (d, 1H, J = 8.1 Hz), 7.61 (d, 1H, J = 7.8 Hz), 7.73 (d, 2H, J = 6 Hz), 11.27 (s, 2H, NH-3-Me-Indole), 11.86 (s, 1H, NH-Indole); δ_C 9.1 (CH_3), 34.1 (Ar_3C), 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 $[M + H]^+$.

We are extremely grateful to the Director, IICB, for laboratory facilities, the Council of Scientific and Industrial Research (CSIR) for awarding fellowship to S. Naskar, A. Hazra, P. Paira and K. B. Sahu and also to Dr V. S. Giri, Dr. R. Mukherjee and Mr K. Sarkar for recording the spectra.

Received 18 March 2008; accepted 18 July 2008
Paper 08/5166 doi:10.3184/030823408X361101
Published online: 10 October 2008

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