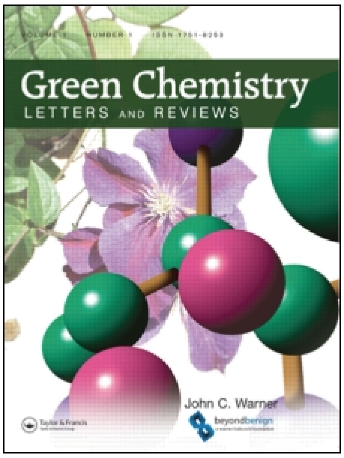


Green Chemistry Letters and Reviews
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t748292817

PEG-600: a facile and eco-friendly reaction medium for the synthesis of N-alkyl derivatives of indole-3-carboxyaldehyde

P. K. Dubey[a]; M. Venkatanarayana[a]
[a] Department of Chemistry, JNTUH College of Engineering, Hyderabad, Andhra Pradesh, India

To cite this Article Dubey, P. K. and Venkatanarayana, M.(2010) 'PEG-600: a facile and eco-friendly reaction medium for the synthesis of N-alkyl derivatives of indole-3-carboxyaldehyde', Green Chemistry Letters and Reviews, 3: 4, 257 — 261
To link to this Article: DOI: 10.1080/17518251003749379
URL: http://dx.doi.org/10.1080/17518251003749379

Green Chemistry Letters and Reviews
Vol. 3, No. 4, December 2010, 257–261

Taylor & Francis
Taylor & Francis Group

RESEARCH LETTER

PEG-600: a facile and eco-friendly reaction medium for the synthesis of N-alkyl derivatives of indole-3-carboxyaldehyde

P.K. Dubey* and M. Venkatanarayana

Department of Chemistry, JNTUH College of Engineering, Kukatpally, Hyderabad 500 085, Andhra Pradesh, India

(Received 17 December 2009; final version received 1 March 2010)

A facile and eco-friendly methodology for the synthesis of N-alkyl/aralkyl derivatives of indole & indole-3-carboxyaldehydes mediated by polyethylene glycol as an efficient and green solvent is described.

Keywords: Indole-3-aldehyde; PEG-600; alkylation

Introduction

Indole and its myriad of derivatives continue to capture the attention of synthetic organic chemists due to their profound biological activity (*1*). In view of their importance as potential pharmacological compounds we intended to prepare N-substituted derivatives of simple indoles and indole-3-aldehydes. Herein we report the results of those studies in this communication.

Previous methods used to synthesize N-substituted indoles (*2–5*) and indole-3-aldehydes (*6*) were associated with long reaction times, tedious workup procedures and low yields. In addition, the reaction media were found to be solvents such as benzene, acetonitrile, and dimethyl formamide; all of which are toxic, carcinogenic or non-eco-friendly in nature. Hence, it was our endeavor to replace the reaction medium and develop an eco-friendly methodology for syntheses of N-substituted derivatives in reasonably good yields.

Results and Discussion

Polyethylene glycol (PEG-600) promoted reactions (*7–10*) have attracted attention of chemists due to their ease of workup, the ability to act as phase transfer catalysts and their inexpensive and eco-friendly nature. Hence, we explored the possibilities of exploiting the versatile features of this (PEG-600) green solvent. In this connection, we are reporting a synthesis of N-substituted indole-3-aldehydes in the presence of PEG-600 as a facile and versatile reaction medium at 120–130°C without additional usage of any base.

Earlier it was reported (*11*) from our lab that the reaction of indole-3-carboxyaldehyde with alkylating agents in the presence of K_2CO_3 as a base and TEBAC as phase transfer catalyst in acetonitrile/dimethylformamide reaction medium for 4–6 hrs at room temperature resulted in the formation of the corresponding N-alkyl derivatives of indole-3-aldehyde in good to moderate yields. When we replace the reaction medium with PEG-600 without additional usage of base the time taken to complete the reaction decreased to 2–3 hrs, also resulting in higher yields. In order to compare the rate of the reaction in PEG-600, we carried out the reaction in different solvents (Table 1).

PEG-600 is a very effective solvent which dissolves the substrate (i.e. indole-3-carboxyaldehyde) and the reagent (i.e. alkylating agent) bringing them together thereby providing an effective means for chemical reaction to occur. Further, PEG-600 is able to extract the hydrogen from the − NH of indole-3-carboxyldehyde and is able to retain it by chelation through several lone pairs of electrons in its oxygen containing chain. This role of PEG-600 is very similar to that of proton sponge (i.e. 1, 8-dimethylaminonaphthalene) which is a very strong base due to its ability to extract hydrogen from an acidic substrate and then retain it in its claws by chelation through lone pair of electrons on the two nitrogen atoms of proton sponge.

Stimulated by the ease of reaction, various indoles and indole-3-aldehyde derivatives were made to react with different alkylating agents in the presence of PEG-600, to yield N-alkyl derivatives in excellent yields (Table 2 and Table 3). In conclusion, we have developed an inexpensive, fast, and eco-friendly

---

*Corresponding author. Email: venkatphdm@gmail.com

ISSN 1751-8253 print/ISSN 1751-7192 online

DOI: 10.1080/17518251003749379
http://www.informaworld.com

Table 1. Rate of reaction in different solvents.

Entry	Solvent	Time (hr)	Temperature (°C)	Yield (%)
1	PEG-600	2	120–130	94
2	PEG-600/CH_3CN	2	100	85
3	CH_3CN/K_2CO_3/TBAB	5	RT	65
4	DMF/K_2CO_3/TBAB	6	RT	60
5	MeOH	24	RT	No reaction
6	EtOH	24	RT	No reaction
7	$CHCl_3$	24	RT	No reaction

methodology for the synthesis of N-substituted derivatives of indole and indole-3-aldehydes using PEG-600 as the reaction medium.

Indole-3-aldehyde was synthesized from indole using Vilsmeir-Haack formylation (*12*). The obtained product was heated with the suitable alkylkating agent (DMS, DES, $PhCH_2Cl$, etc.) in PEG-600 as a reaction medium at 120–130°C without additional usage of any base followed by a simple workup to yield the N-alkyl derivatives of indole-3-aldehyde. The reaction was extended to other indole-3-aldehyde derivatives to build the library of N-substituted indole-3-aldehyde

Table 2. Analytical and spectral data of N-alkyl derivatives of indole-3-carboxyaldehyde.

S. No.	Analytical and spectral data
IIIb	IR(KBr) 1645 cm^{-1} due to $-$C$=$O of $-$CHO group; ^{1}H NMR (300 MHz, DMSO/d_6/TMS, Δ ppm) 1.43 (t, 3**H**, $J=7.4$ Hz, $-$N**CH$_3$**), 4.08 (q, 2**H**, $J=7.4$ Hz, $-$**CH$_2$**), 7.20$-$7.40 (m, 2**H**, aromatic), 7.62 (m, 1**H**, aromatic), 8.10 (m, 1**H**, aromatic), 8.39 (s, 1**H**, **H**-2), 9.95 (s,1**H**, $-$CHO); MS *m/z* 171 (M$^+$); [Found: C: 76.26, H: 6.42, N: 8.07, O: 9.26, $C_{11}H_{11}NO$ requires C: 76.28, H: 6.40, N: 8.09, O: 9.24%].
IIIe	IR(KBr) 1645 cm^{-1} due to $-$C$=$O of–CHO group; ^{1}H NMR (300 MHz, DMSO/d_6/TMS, Δ ppm) 1.42 (t, 3H, $-$CH$_3$, $J=7.2$ Hz), 4.37 (q, 2**H**, $J=7.2$ Hz, $-$**CH$_2$**), 7.85 (d, 1**H**, $J_{7,6}=8.8$ Hz, **H**-7), 8.15 (dd, 1**H**, aromatic, $J_{6,7}=8.8$ Hz, $J_{6,4}=2.2$ Hz, **H**-6), Δ 8.61 (s, 1**H**, **H**-2), Δ 8.89 (d, 1H, $J_{4,6}=2.2$ Hz, **H**-4), Δ 9.96 (S, 1**H**, $-$CHO); MS *m/z* 216 (M$^+$); [Found: C: 60.55, H: 4.32, N: 9.99, O: 17.13, $C_{11}H_{12}N_2O_3$ requires C: 60.54, H: 4.31, N: 9.97, O: 17.17].
IIIf	IR(KBr) 1645 cm^{-1} due to $-$C$=$O of $-$CHO group; ^{1}H NMR (300 MHz, DMSO/d_6/TMS, Δ ppm) 5.64 (s, 2**H**, $-$**CH$_2$**Ph), 7.27$-$7.36 (m, 5**H**, aromatic), 7.85 (d, 1**H**, $J_{7,6}=8.8$ Hz, **H**-7), 8.15 (dd, 1**H**, aromatic, $J_{6,7}=8.8$ Hz, $J_{6,4}=2.3$ Hz, **H**-6), 8.74 (s, 1**H**, **H**-2), 8.94 (d, 1**H**, $J=2.3$ Hz, **H**-4), 10.02 (s, 1**H**, $-$**CH**); MS *m/z* 280 (M$^+$); $^+$); [Found: C: 68.54, H: 4.33, N: 9.98, O: 17.15, $C_{16}H_{12}N_2O_3$ requires C: 68.56, H: 4.32, N: 9.99, O: 17.13].
IIIi	IR(KBr) 1645 cm^{-1} due to $-$C$=$O of–CHO group; ^{1}H NMR (300 MHz, DMSO/d_6/TMS, Δ ppm) 5.40 (s, 2**H**, $-$**CH$_2$**), 6.84–8.30 (m, 14**H**, aromatic), 9.60 (s, 1**H**, $-$CHO); MS *m/z* 311 (M$^+$); [Found: C: 84.86, H: 5.50, N: 4.50, O: 5.14, $C_{22}H_{17}NO$ requires C: 84.82, H: 5.59, N: 4.49, O: 5.15].
IIIk	IR(KBr) 1645 cm^{-1} due to $-$C$=$O of–CHO group; ^{1}H NMR (300 MHz, DMSO/d_6/TMS, Δ ppm) 1.51 (t, 3**H**,), 3.86 (q, 2**H**), 7.23 (d, 1**H**, $J_{7,6}=8.8$ Hz, **H**-7), 7.45 (dd, 1**H**, $J_{6,7}=8.8$ Hz, $J_{6,4}=2$ Hz, **H**-6), 7.67 (s, 1**H**, **H**-2), 8.47 (d, 1**H**, $J_{4,6}=2$ Hz, **H**-4), Δ 9.96 (s, 1**H**, $-$CHO); MS *m/z* 249 (M$^+$); [Found: C: 52.42, H: 3.99, Br: 31.69, N: 5.54, O: 6.36, $C_{11}H_{10}BrNO$ requires C: 52.41, H: 4.00, Br: 31.71, N: 5.56, O: 6.35].
IIIl	IR(KBr) 1645 cm^{-1} due to $-$C$=$O of–CHO group; ^{1}H NMR (300 MHz, DMSO/d_6/TMS, Δ ppm) 5.12 (s, 2**H**, $-$**CH$_2$**), 7.23–8.8 (9**H**, five phenyl protons$+$three aryl protons$+$one α-proton of the indole) 9.96 (s, 1**H**, $-$CHO); MS *m/z* 313 (M$^+$); [Found: C: 61.17, H: 3.85, Br: 25.43, N: 4.46, O: 5.09, $C_{16}H_{12}BrNO$ requires C: 61.18, H: 3.86, Br: 25.45, N: 4.45, O: 5.10].
IIIm	IR(KBr) 1645 cm^{-1} due to $-$C$=$O of–CHO group; ^{1}H NMR (300 MHz, DMSO/d_6/TMS, Δ ppm) 3.73 (s, 3**H**, $-$N**CH$_3$**), 3.86 (s, 3**H**, $-$O**CH$_3$**), 7.23 (d, 1**H**, $J_{7,6}=8.8$ Hz, **H**-7), 7.45 (dd, 1**H**, $J_{6,7}=8.8$ Hz, $J_{6,4}=2$ Hz, **H**-6), 7.67 (s, 1**H**, **H**-2), 8.47 (d, 1**H**, $J_{4,6}=2$ Hz, **H**-4), 9.96 (s, 1**H**, $-$CHO); MS *m/z* 189 (M$^+$); [Found: C: 69.830, H: 5.85, N: 7.41, O: 16.90, $C_{11}H_{11}NO_2$ requires C: 69.831, H: 5.54, N: 7.42, O: 16.89].
IIIn	IR(KBr) 1645 cm^{-1} due to $-$C$=$O of–CHO group; ^{1}H NMR (300 MHz, DMSO/d_6/TMS, Δ ppm) 3.89 (q 2**H**, $-$N**CH$_2$**), 1.49 (t 3**H**, $-$**CH$_3$**), 7.23 (d, 1**H**, $J_{7,6}=8.8$ Hz, **H**-7), 7.45 (dd, 1**H**, $J_{6,7}=8.8$ Hz, $J_{6,4}=2$ Hz, **H**-6), 7.67 (s, 1**H**, **H**-2), 8.47 (d, 1**H**, $J_{4,6}=2$ Hz, **H**-4), 9.96 (s, 1**H**, $-$CHO); MS *m/z* 201 (M$^+$); [Found: C: 70.93, H: 6.46, N: 6.87, O: 15.76, $C_{12}H_{13}NO_2$ requires C: 70.94, H: 6.86, N: 6.88, O: 15.75].
IIIo	IR(KBr) 1645 cm^{-1} due to $-$C$=$O of $-$CHO group; ^{1}H NMR (300 MHz, DMSO/d_6/TMS/Δ ppm): 3.78 (s, 3**H**, $-$O**CH$_3$**), 5.14 (s, 2**H** –**CH$_2$**), 7.23–8.76 (9**H**, five phenyl protons$+$three aryl protons$+$one α-proton of the indole), 9.96 (s, 1**H**, $-$CHO); MS *m/z* 265 (M$^+$); [Found: C: 76.95, H: 5.71, N: 5.27, O: 12.07].

Table 3. Characterization data of compounds prepared.

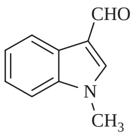
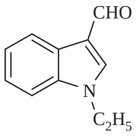
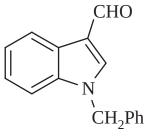
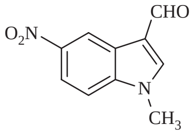
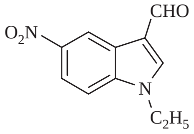
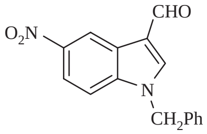
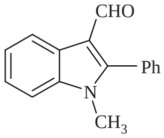
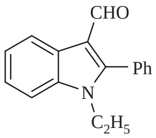
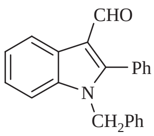
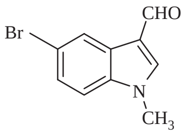
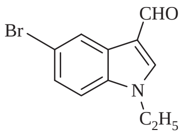
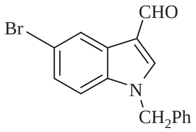
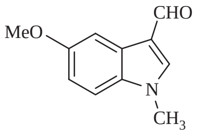
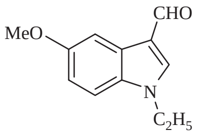
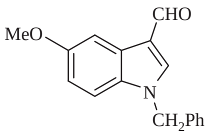
S. No.	Compound	Yield	MP (°C)
IIIa		92	69 (Lit. 68–70) (*15*)
IIIb		92	98–100
IIIc		88	106–08
IIId		94	196–98 (*16*)
IIIe		92	174–76
IIIf		93	178–80
IIIg		92	123 (Lit. 122–124) (*13*)
IIIh		95	101 (Lit. 99–100) (*13*)
IIIi		95	176–78

Table 3 (*Continued*)

S. No.	Compound	Yield	MP (°C)
IIIj		85	136 (Lit. 134–36) (*14*)
IIIk		90	175–77
IIIl		91	181–83
IIIm		94	157–59
IIIn		90	152–55
IIIo		92	163–65

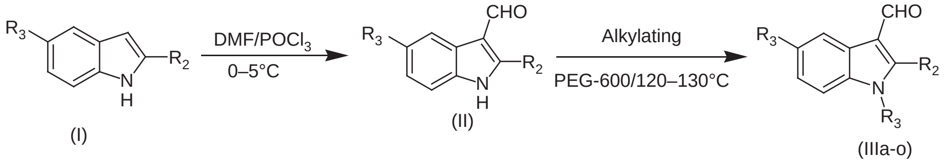
derivatives. All the above compounds were characterized by ^{1}H NMR, IR, and CI mass spectra.

Experimental

Melting points were measured in open capillary tubes and are uncorrected. TLC was done on glass plates coated with Silica Gel – G and spotting was done using iodine or UV lamp. IR spectra were recorded using Perkin Elmer model-446 FTIR in KBr. ^{1}H NMR spectra were recorded on a Gemini-2000 and AV-400 operating at 200 and 400 MHz, respectively.

Preparation of II from I

To DMF (1.6 ml, 22 mmol) cooled in ice-water, was added $POCl_3$ (0.05 ml, 5.5 mmol) during 30 minutes. The solution was stirred at the same temperature for an additional 15 minutes until an orange syrupy



Scheme 1. Synthesis of N-alkyl derivatives of indole-3-carboxyaldehyde mediated by PEG-600.

liquid was formed. To this, I (5 mmol) in DMF (10 ml) was added over 30 minutes. The solution was stirred at 0–5°C for an additional 20 minutes and brought to RT. The mixture was stirred at RT for 45 minutes. After this period, the solution was poured into crushed ice and neutralized with three portions of NaOH (4 g in 20 ml), the two portions being added drop wise maintaining the pH at acidic and third one was added in one lot and solution was heated on a water bath for period of 1–2 minutes when a solid began to separate. The separated solid was filtered, washed with water and dried to obtain crude **II**. The latter was recrystalized from ethanol to obtain pure **II**.

Preparation of III from II: (General procedure)

About 5 mM of the appropriate indole-3-aldehyde derivative was taken in 50 ml round bottom flask containing 25 ml of PEG-600. To this was added the appropriate alkylating agent (DMS, DES, $PhCH_2Cl$, etc.) (7.5 mmol) dropwise at RT. The reaction mass was refluxed for 2 hr at 120–130°C. At the end of this period, the reaction mass was poured into ice cold water. The separated solid was filtered, washed with excess water and dried to obtain the crude. The latter were recrystalized from methanol to obtain pure **III**.

Acknowledgements

The authors are highly indebted to University Grants Commission, Govt. of India, New Delhi, for providing financial support. They are also thankful to the authorities of Jawaharlal Nehru Technological University, Hyderabad, for providing laboratory facilities.

References

(1) Sundberg, R.J. *The Chemistry of Indoles*; Academic Press: New York, London, 1970.

(2) Plieninger, H. *Chem. Ber.* **1954**, *87*, 127–128.

(3) Cornforth, R.H.; Robinson, R. *J. Chem. Soc.* **1940**, 680–683.

(4) Pederson, E.B.; Zahran, M.A.; Afify, H.M.; Nielsen, C. *J. Chem. Res.* (S) **2001**, *9*, 101–104.

(5) Chauhan, S. *Indian J. Chem.* **1994**, *33B*, 32–37.

(6) Smith, G.F. *J. Chem. Soc.* **1954**, 3842–3846.

(7) Dicekerson, T.J.; Janda, K.D. *Chem. Rev.* **2002**, *102*, 3325–3344.

(8) Kamal, A.; Reddy, D.R.; Rajender. *Tetrahedron Lett.* **2005**, *46*, 7951–7953.

(9) Babasaheb Bandgar, P.; Balaji Korea, L.; Sachin Patil, A.; Sunita Bandgar, B.; Hemant Chavan, V.; Baliram Hote, S. *Aust. J. Chem.* **2008**, *61* (9), 700–703.

(10) Mahalle, S.; Dinesh, L.; Ramrao, M. *Green Chem. Lett. Rev.* **2008**, *2*, 103–106.

(11) Dubey, P.K.; Balaji, B.; Venkatanarayana, M. *Indian J. Heterocycl. Chem.* **2006**, *15*, 205–208.

(12) James, P.N.; Snyder, H.R. *Org. Synth.* **1959**, *39*, 30–33.

(13) Blume, R.C.; Lindwall, H.G. *J. Org. Chem.* **1945**, *10*, 255–258.

(14) Noland, W.E.; Reich, C. *J. Org. Chem.* **1967**, *32*, 828–832.

(15) Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915–13928.

(16) Da Settimo, A.; Saettone, M.F. *Tetrahedron* **1965**, *21*, 1923–1929.