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ARTICLE

Polyethylene Glycol (PEG-400) as an Efficient and Recyclable Reaction Medium for Four-Component Coupling One-Pot Synthesis of Functionalized Pyrroles under Catalyst-free Conditions

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Asian Journal of Organic & Medicinal Chemistry

Volume: 1 Year: 2016
Issue: 2 Month: April-June
pp: 61-65
DOI: http://dx.doi.org/10.14233/ajomc.2016.AJOMC-P18

Received: 6 June 2016
Accepted: 15 June 2016
Published: 2 July 2016

ABSTRACT

Polyethylene glycol (PEG) was found to be an effective and non-toxic reaction medium for the one-pot synthesis of functionalized pyrroles under catalyst-free conditions in excellent yields. Environmental acceptability, low cost, high yields and recyclability of the PEG are the important features of this protocol.

KEYWORDS

Functionalized pyrroles, 1,3-Dicarbonyl compounds, Amines, Aromatic aldehydes and Nitroalkanes, Polyethylene glycol, Catalyst-free conditions.

INTRODUCTION

Pyrrole ring ranks among the most important heterocyclic compounds as it is a structural motif of various bioactive natural products [1,2] and pharmaceutical agents [3-5]. Pyrroles also serve as valuable intermediates in organic synthesis [6,7]. Furthermore, functionally divergent pyrroles have been widely used as antitumor [8], anti-inflammatory [9,10], antibacterial [10,11], antioxidant [12] and antifungal agents [13]. In addition various pyrrole derivatives are widely used as building blocks and organic conducting compounds in science [14,15]. Consequently, a wide range of procedures have been devised for the synthesis of pyrroles [16-21].

The synthesis of pyrroles and their derivatives is usually achieved by well-known methods like Hantzsch or Knorr or Paal Knorr reaction [22-27]. The synthesis of pyrroles and their derivatives through multicomponent reactions (MCRs) has been demonstrated by numerous research groups. For instant, the synthesis of tetra substituted pyrrole has been reported by Jana and co-workers [28] by employing four-component reaction catalyzed by $FeCl_3$. Although several protocols have been developed for the synthesis of functionalized pyrroles [28], many of the methods possess drawbacks such as harsh reaction conditions, tedious experimental procedures, unsatisfactory yields, long reaction times or use of expensive and moisture sensitive catalysts. Hence, there is a

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need for the rapid and efficient method of the synthesis of substituted pyrroles under catalyst-free conditions.

In recent years, polyethylene glycol (PEG) has emerged as a powerful phase-transfer catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, PEG is an inexpensive, easy to handle, thermally stable, non-toxic and recyclable medium for various organic transformations [29-33]. In continuation of our interest in the field of PEG-mediated synthesis of heterocyclic compounds under catalyst-free conditions, we report herein the synthesis of functionalized pyrroles *via* Tandem Michael addition-cyclization using PEG-400 as a recyclable medium without any additional organic solvent and catalyst. To the best of our knowledge there are no previous reports on the synthesis of functionalized pyrroles using PEG-400 as a reaction medium under catalyst-free conditions (**Scheme-I**).

EXPERIMENTAL

General procedure for the synthesis of functionalized pyrroles by using PEG as reaction medium (Scheme-I): A mixture of the aldehyde (1 mmol), amine (1.5 mmol), 1,3-dicarbonyl compounds (1 mmol) and nitromethane (1 mL) was taken in 5 mL of polyethylene glycol and stirred at 85 °C for the appropriate time. After completion of the reaction, as monitored by TLC, the reaction mass was extracted with ethyl acetate (3 5 mL) and separated PEG. The combined organic layers were evaporated under reduced pressure and the crude product was purified by column chromatography using silica gel (60-120 mesh) and hexane/EtOAc, 9:1). The recovered PEG was vacuum dried and reused for three cycles without significant loss of activity.

1-(1-Benzyl-2-methyl-4-phenyl-1*H*-pyrrol-3-yl)-ethanone (1): Orange yellow sticky liquid (80 % yield) IR (neat, cm^{-1}): 3062, 3030, 2936, 1638, 1599, 1512, 1419, 1358, 1287, 1189, 1139, 1030, 953, 909, 739, 706. ^{1}H NM. 13 (d, *J* = 7.2 Hz, 2H), 7.32-7.40 (m, 8H), ppm.^{13}CNMR ($CDCl_3$, 75 MHz): δ 11.6, 29.7, 31.1, 50.3, 120.1, 122.1, 125.9, 126.4, 126.7, 126.7, 127.8, 128.2, 128.9, 129.4, 135.1, 136.3, 136.6, 197.5.ppm. MS (EI): *m/z* 289 (M^+ +1)

1-[1-Benzyl-2-methyl-4-(*p*-tolyl)-1*H*-pyrrol-3-yl]-ethanone (2): Orange yellow sticky liquid (85 % Yield): IR (neat, cm^{-1}): 3030, 2920, 2860, 1720, 1654, 1556, 1517, 1413, 1353, 1276, 1178, 1134, 1035, 942, 827, 706. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.09 (s, 3H) 2.41 (s, 3H), 2.09 (s.3H) 2.47 (s.3H), 5.08 (s, 2H), 6.55 (s, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.19-7.27 (m, 4H), 7.32-7.39 (m, 3H), ppm. ^{13}CNMR ($CDCl_3$, 75 MHz) δ 11.6, 21.1, 29.7, 31.1, 50.3, 120.0, 122.1, 125.8.9, 126.7.3, 127.8, 128.9, 129.2, 133.3, 135.0, 136.3, 136.6, 197.6 ppm. MS (EI): *m/z* 304 (M^+ +1).

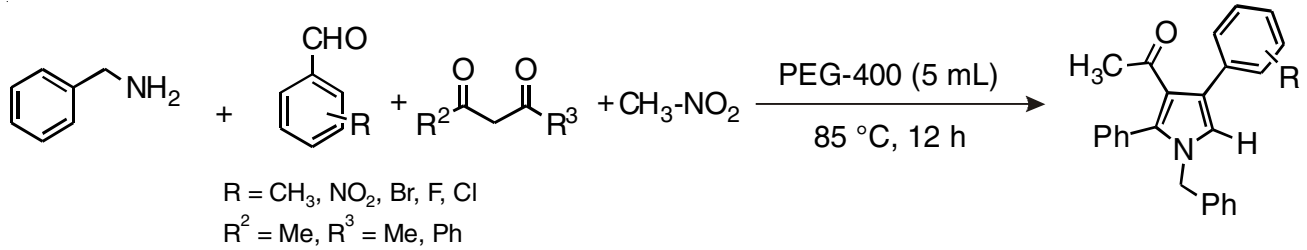
1-[1-Benzyl-2-methyl-4-(4-nitrophenyl)-1*H*-pyrrol-3-yl]ethanone (3): Deep red sticky liquid (90 %) Yield. IR (neat, cm^{-1}): 3062, 2925, 2849, 1649, 1599, 1506, 1435, 1342, 1183, 1106, 1013, 947, 860, 761, 706. ^{1}HNMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), 2.45 (s, 3H), 5.11 (s, 2H), 6.68 (s, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.35-7.40 (m, 3H), 7.35 (d, *J* = 8.4 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 31.1, 50.5, 121.1, 122.1, 123.5, 123.8, 123.5, 126.6, 128.0, 129.0, 129.4, 135.8, 136.0, 143.2, 146.3, 196.6 ppm. MS (EI): *m/z* 334 (M^+ +1).

1-[1-Benzyl-4-(4-bromophenyl)-2-methyl-1*H*-pyrrol-3-yl]ethanone (4): Orange sticky liquid (85 % Yield). IR (neat, cm^{-1}): 3024, 2920, 2854, 1649, 1550, 1506, 1413, 1353, 1282, 1178, 1134, 1008, 953, 832, 734, 701. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.09 (s, 3H), 2.45 (s, 3H), 5.07 (s, 2H), 6.56 (s, 1H), 7.10-7.12 (m 2H), 7.21-7.23 (m 2H), 7.31-7.38 (m, 3H), 7.48-7.50 (m, 2H) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz) δ 11.6, 31.1, 50.3, 120.2, 120.7, 122.0, 124.5, 126.7, 127.9, 129.0, 130.9, 131.3, 135.3, 135.4, 136.4, 197.0ppm. MS (EI): *m/z* 367 (M^+ + 1).

1-[1-Benzyl-4-(2-bromophenyl)-2-methyl-1*H*-pyrrol-3-yl]ethanone (5): Orange yellow sticky liquid (85 % Yield). IR (neat, cm^{-1}): 3057, 2915, 1649, 1512, 1413, 1347, 1183, 1134, 1019, 942. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.96 (s, 3H), 2.50 (s, 3H), 5.10 (s, 2H), 6.52 (d, *J* = 3.2 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 7.23 (s, 1H), 7.31-7.39 (m, 5H) 7.66 (d, *J* = 8 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.5, 50.5, 121.2, 121.3, 124.0, 124.2, 126.6, 127.3, 127.6, 127.8, 129.0, 129.6, 131.2, 132.4, 132.4, 135.0, 136.4, 136.7, 139.8, 193.5 ppm. MS (EI): *m/z* 367 (M+ $^+$1).

1-[1-Benzyl-4-(2-fluorophenyl)-2-methyl-1*H*-pyrrol-3-yl]ethanone (6): Orange yellow sticky liquid 6l (88 % Yield). IR (neat, cm^{-1}): 3112, 3062, 3024, 2914, 1649, 1550, 1517, 1452, 1408, 1353, 1216, 1134, 1090, 1030, 947, 761, 520. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.97 (d, *J* = 4.1Hz, 3H), 2.36 (d, *J* = 4 Hz, 3H), 4.97 (s, 2H), 6.49 (s, 1H), 6.99-7.27 (m, 9H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.7, 30.0, 50.3, 115.4, 115.6, 118.3, 121.0, 122.3, 124.0, 124.0, 124.1, 124.2, 126.7, 127.8, 128.9, 129.3, 131.7, 131.7, 135.3, 136.5, 158.8, 161.2, 196.7 ppm. MS (EI) : *m/z* 307 (M^+ +1).

1-[1-Benzyl-4-(3-chlorophenyl)-2-methyl-1*H*-pyrrol-3-yl]ethanone (7): Deep red sticky liquid (87 % Yield). IR (neat, cm^{-1}): 3057, 3019, 2920, 1643, 1594, 1501, 1413, 1336, 1271, 1178, 1128, 1068, 953, 876, 789, 728, 690. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10-7.27 (m, 7H), 6.98-700 (t, *J* = 8 Hz, 2H), 7.24-7.35 (m, 7H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.6, 31.1, 50.3, 120.4, 122.0, 124.4, 126.7, 127.6, 127.8, 127.9, 128.2, 129.0, 129.1, 129.3, 129.4, 134.0, 135.4, 136.4, 138.2, 197.0 ppm. MS (EI): *m/z* 323 (M^+ +1).



Scheme-I

1-[1-Benzyl-4-(2-fluorophenyl)-2-phenyl-1*H*-pyrrol-3-yl]ethanone (8): Orange yellow sticky liquid (85 % Yield). IR (neat, cm^{-1}): 3063, 3030, 2920, 2838, 2350, 1731, 1643, 1523, 1452, 1419, 1287, 1221, 1079, 1024, 920, 805, 750, 728, 695. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.03 (s, 3H), 5.03 (s, 2H), 6.45-6.77 (m, 2H), 6.92-6.99 (m, 1H), 7.00-7.03 (m, 1H), 7.48-7.54 (m, 5H), 7.56-7.49 (m, 4H), 7.86-7.88 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.4, 50.6, 115.0, 115.2, 118.8, 129.0, 129.6, 130.9, 130.9, 131.5, 135.0, 136.7, 139.6, 158.0, 160.4, 193.7 ppm. MS (EI): *m/z* 369 (M^+ +1).

1-[1-Benzyl-4-(3-chlorophenyl)-2-phenyl-1*H*-pyrrol-3-yl]ethanone (9): Orange yellow sticky liquid (90 % Yield). IR (neat, cm^{-1}): 3063, 2920, 1638, 1605, 1528, 1457, 1424, 1353, 1282, 1216, 1079, 909, 728, 690. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 5.13 (s, 2H), 6.76 (s, 1H), 6.97 (s, 2H), 7.16 (s, 3H), 7.21-7.25 (m, 3H), 7.33-7.42 (m, 4H), 7.70-7.72 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.4, 50.6, 119.9, 120.1, 124.7, 125.5, 126.6, 126.7, 127.8, 127.9, 128.2, 129.0, 129.7, 131.8, 133.6, 135.5, 136.5, 137.0, 139.6, 193.8 ppm. MS (EI): *m/z* 385 (M^+ +1).

1-[1-Benzyl-4-(4-nitrophenyl)-2-phenyl-1*H*-pyrrol-3-yl]ethanone (10): Deep red sticky liquid (85 % Yield). IR (neat, cm^{-1}): 3057, 2920, 1731, 1621, 1594, 1517, 1441, 1413, 1276, 1199, 1068, 1019, 904, 734, 695, 515. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.13 (s, 3H), 2.44 (s, 3H), 5.10 (s, 2H), 6.66 (s, 1H), 7.10 (d, *J* = 6.9 Hz, 2H), 7.27-7.40 (m, 3H), 7.47 (d, *J* = 8.5 Hz, 2H), 8.21 (d, *J* = 8.5 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.3, 50.5, 119.4, 125.5, 126.7, 127.6, 127.8, 127.8, 128.3, 128.9, 129.8, 131.6, 135.1, 136.7, 139.6, 194.0 ppm. MS (EI) : *m/z* 396 (M^+ +1).

1-[1-Benzyl-4-(4-bromophenyl)-2-phenyl-1*H*-pyrrol-3-yl]ethanone (11): Orange yellow sticky liquid (85 % Yield). IR (neat, cm^{-1}): 3057, 3024, 2914, 1632, 1517, 1419, 1287, 1199, 1068, 1008, 915, 832, 728, 701. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.31 (s, 3H), 5.12 (s, 2H), 6.74 (s, 1H), 6.99-7.01 (m, 2H) 7.14-7.16 (m, 2H), 7.19-7.25 (m, 4H), 7.33-7.39 (m, 4H)7.70-7.72 (m, 2H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.4, 50.6 119.5, 119.6, 120.1, 124.9, 126.7, 127.8, 128.4, 129.0, 129.7, 129.8, 130.9, 131.9, 134.1, 135.3, 136.6, 139.5, 193.8 ppm. MS (EI) : *m/z* 428 (M^+ +1).

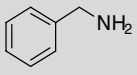
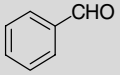
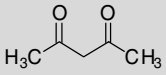
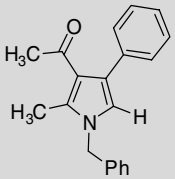
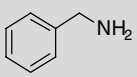
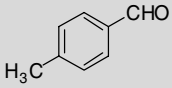
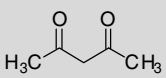
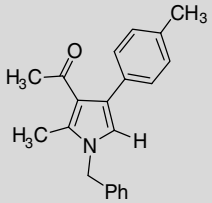
1-[1-Benzyl-2-phenyl-4-(*p*-tolyl)-1*H*-pyrrol-3-yl]-ethanone (12): Orange yellow sticky liquid 6d (85 % Yield). IR (neat, cm^{-1}): 3057, 3024, 2920, 2865, 2356, 1693, 1627, 1594, 1517, 1446, 1424, 1347, 1282, 1210, 1117, 1079, 1030, 898, 821, 723, 695. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.22 (s, 3H), 2.32 (s, 3H), 5.13 (s, 2H), 6.73 (s, 1H), 6.90-6.91 (m, 2H), 7.04-7.05 (m, 2H), 7.15-7.17 (m, 2H), 7.21 (t, *J* = 8 Hz, 2H), 7.32-7.35 (m, 2H), 7.38-7.39 (m, 2H), 7.73-7.74 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.3, 20.9, 50.3, 119.3, 120.2, 126.7, 127.7, 127.8, 128.2, 128.5, 128.9, 129.8, 131.6, 132.1, 134.8, 135.1, 136.8, 139.6, 194.1 ppm. MS (EI) : *m/z* 365 (M^+ +1).

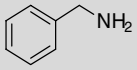
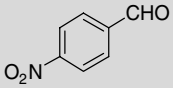
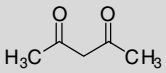
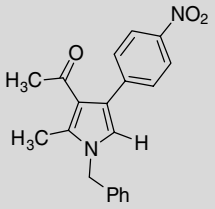
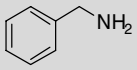
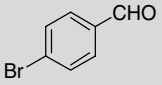
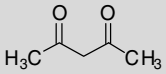
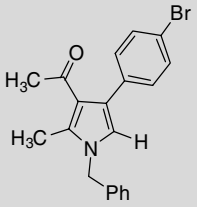
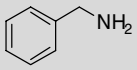
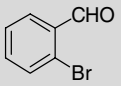
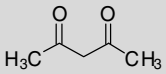
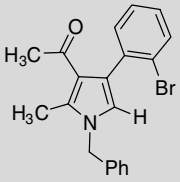
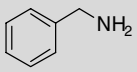
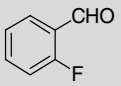
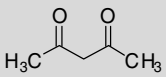
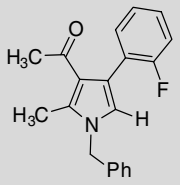
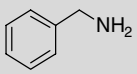
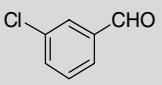
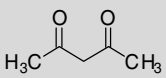
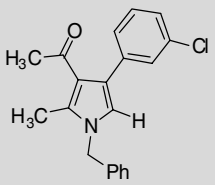
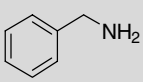
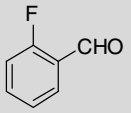
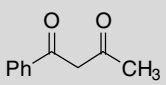
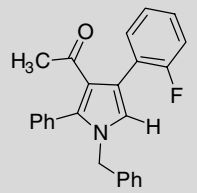
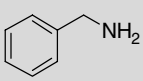
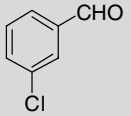
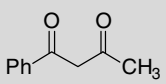
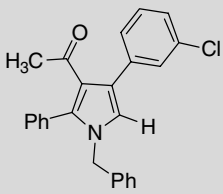
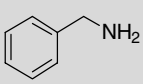
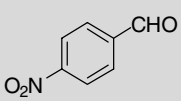
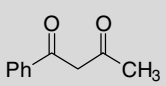
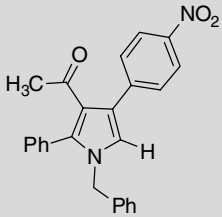
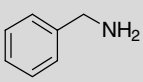
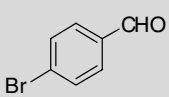
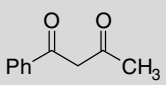
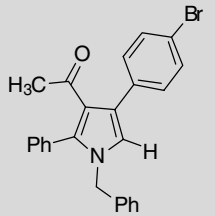
1-[1-Benzyl-4-(2-bromophenyl)-2-phenyl-1*H*-pyrrol-3-yl]ethanone (13): Orange yellow sticky liquid (76 % Yield). IR (neat, cm^{-1}): 3052, 3024, 2915, 1715, 1627, 1523, 1408, 12387, 1210, 1030, 915, 739, 695. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.39 (s, 3H), 5.15 (s, 2H), 6.74 (s, 1H), 6.85-6.89 (m, 1H), 7.02-7.05 (m, 1H), 713-7.18 (m, 5H), 7.24-7.28 (m, 1H), 7.31-7.41 (m, 4H)7.65-7.67 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.5, 50.5, 121.2, 121.3, 124.0, 124.2, 126.6, 127.6, 127.8, 129.0, 129.6, 131.2, 132.4, 132.4, 136.4, 136.7, 139.8, 193.5 ppm. MS (EI) : *m/z* 428 (M^+ +1).

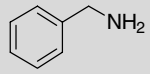
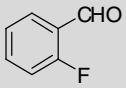
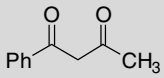
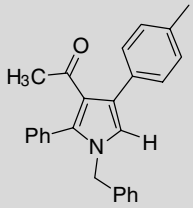
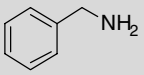
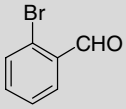
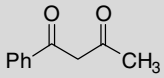
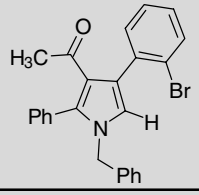
RESULTS AND DISCUSSION

The generality of this reaction was investigated by the synthesis of various functionalized pyrroles derivatives using a variety of aromatic aldehydes, amine, active methylene compounds and nitroalkanes. The result are presented in Table-1. In general, all the reactions were very clean and the functionalized pyrroles derivatives were obtained in high yields. Notably, aldehydes bearing a strong electron-withdrawing groups (NO_2) (Table-1, entries 3,10) at the *para* position gave the desired products in quantitative yields in 12 h and also the aldehyde bearing electron-donating groups (F, Br, Me), (Table-1, entries 4,6,8,11,12) at the *para*-position gave the desired products in high yields. Thus, variation of aldehydes was accommodated comfortably in this four-component coupling reaction, generating moderate to high yields of the functionalized pyrroles. The structures of all the products were determined from their analytical and spectral (IR, ^1H NMR

TABLE-1
PEG-400 MEDIATED SYNTHESIS OF FUNCTIONALIZED PYRROLES

Entry	Amine	Aldehyde	1,3-Dicarbonyl compound	Product	Time (h)	Yield (%)
1					10	80
2					10	85

Entry	Amine	Aldehyde	1,3-Dicarbonyl compound	Product	Time (h)	Yield (%)
3					12	90
4					10	85
5					10	85
6					12	88
7					12	87
8					10	85
9					12	90
10					10	85
11					10	85

Entry	Amine	Aldehyde	1,3-Dicarbonyl compound	Product	Time (h)	Yield (%)
12					12	88
13					12	87

All reactions were performed with amines (1 equiv), aldehydes (1 equiv), 1,3-dicarbonyl compounds and nitromethane in PEG-400 (5 mL). [b]All reported products were identified by comparison of their melting point, IR, ^{1}H NMR, ^{13}C, NMR, Mass and HRMS. [c]Isolated yields after column chromatography.

and ^{13}C NMR) data and by direct comparison with the authentic samples.

Conclusion

In conclusion, An efficient and facile method is developed for the synthesis of functionalized pyrroles derivatives by treatment of aromatic aldehydes, amine, 1,3-dicarbonyl compounds and nitromethane using PEG as a recyclable medium without the addition of any additive or organic cosolvent. The mild reaction conditions, less expensive of reaction medium, operational simplicity and high yields are the advantages of the protocol.

ACKNOWLEDGEMENTS

The authors are thankful to CSIR, for their kind help and support and UGC-CSIR, New Delhi for financial assistance.

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