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Polyethylene glycol (PEG-400) as an efficient and recyclable reaction medium for one-pot synthesis of polysubstituted pyrroles under catalyst-free conditions

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ABSTRACT

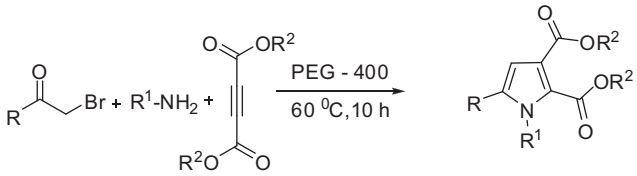
Polyethylene glycol (PEG) was found to be an inexpensive non-toxic and effective medium for the one-pot synthesis of highly functionalized pyrroles. Utilizing this protocol various pyrrole derivatives were synthesized in excellent yields. Environmental acceptability, low cost, high yields, and recyclability of the PEG are the important features of this protocol.

Pyrrole moieties are the most important heterocyclic compounds found in various bioactive natural products[1] and pharmaceutical agents.[2] They have also been recognized as versatile synthetic intermediates in organic synthesis.[1a,3] These derivatives are used as organic conducting materials.[4]

Although several protocols have been developed for the synthesis of pyrrole derivatives,[5] many of the methods are associated with various drawbacks, such as harsh reaction conditions, tedious experimental procedures, unsatisfactory yields, and long reaction times and usage of expensive and moisture sensitive catalysts. Hence, there is a need for a rapid and efficient method for the synthesis of pyrrole derivatives under catalyst-free conditions.

In recent years, polyethylene glycol (PEG) has emerged as a powerful phase transfer catalyst and is utilized in many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable in various organic transformations, such as synthesis of β-amino sulfides, 2-substituted benzimidazoles, bis-benzimidazoles, 3,4-dihydropyrimidinones, β-keto sulfides, and dibenz[*b,f*]-1,4-oxazapine etc.[6] This inspired us to focus on the aspect of the synthesis of biologically active pyrrole derivatives under catalyst-free conditions by using PEG as an eco-friendly and recyclable medium. Herein we report the synthesis of pyrrole derivatives by using PEG-400 as a recyclable medium without adding any organic solvent and catalyst. To the best of our knowledge there are no reports for the synthesis of pyrrole derivatives by using PEG-400 as a reaction medium under catalyst-free conditions (Scheme 1).

The generality of this reaction was investigated for the synthesis of various pyrrole derivatives by using a variety of phenacyl bromides and different anilines with dialkylacetylene dicarboxylates (Table 1). In general, all the reactions were very clean, and the pyrrole derivatives were obtained in high yields. Phenacyl bromides, bearing electron-withdrawing groups (Br, NO_2) at the *para*-position gave the desired products in quantitative yields in 10 h, and also the amines bearing electron-donating groups (Me, OMe), and electron- withdrawing groups (F) at the *para*-position gave the desired products in high yields. Results show that the substitution groups did not play significant role in governing the reactivity of the substrate. In the case of chlorides, only trace amount of the pyrrole derivatives are obtained (Table 1, entry 1). Aliphatic amines instead of aromatic amines gave the desired product in moderate yields (Table 1, entries 14–17). However, the reaction



Scheme 1.

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Table 1

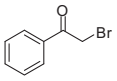
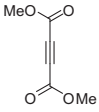
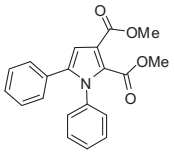
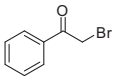
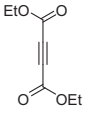
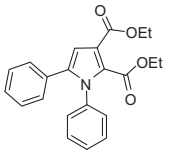
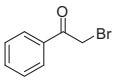
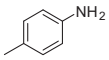
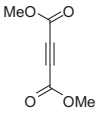
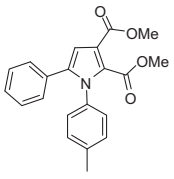
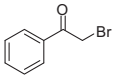
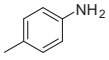
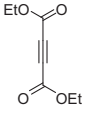
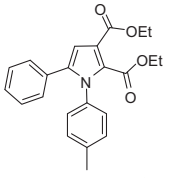
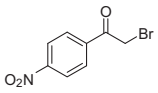
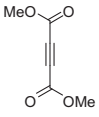
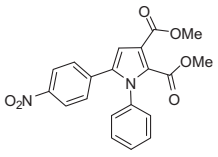
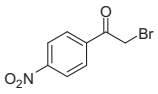
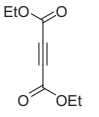
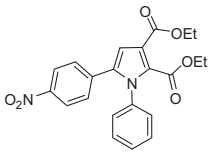
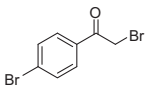
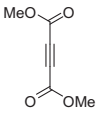
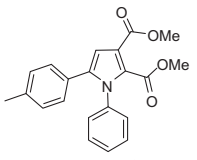
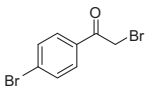
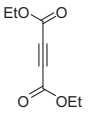
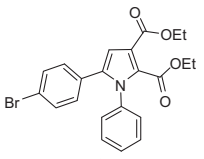
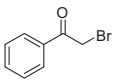
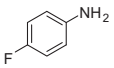
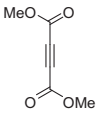
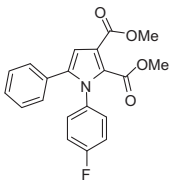
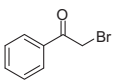
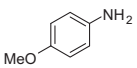
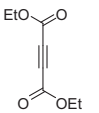
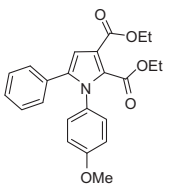
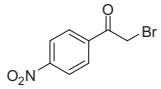
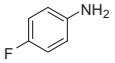
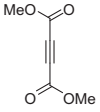
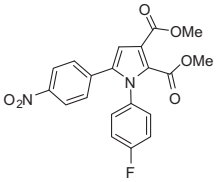
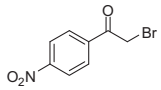
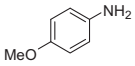
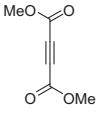
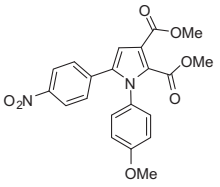
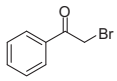
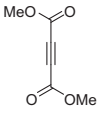
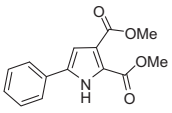
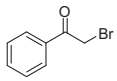
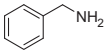
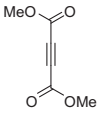
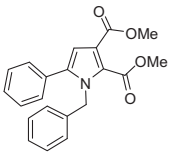
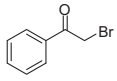
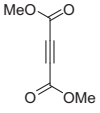
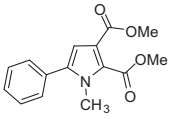
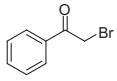
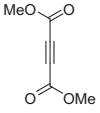
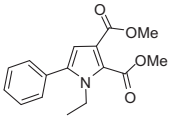
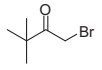
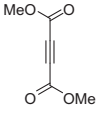
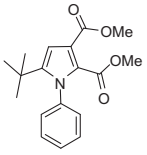
Entry	Halides	Amines	Acetylene dicarboxylates	Product[a]	Yield[b] (%)
1 2					89
3					89
4					85
5					84
6					81
7					80
8					83
9					81
10					80
11					88

Table 1 (*continued*)

Entry	Halides	Amines	Acetylene dicarboxylates	Product[a]	Yield[b] (%)
12					82
13					84
14		NH_4OAC			41
15					75
16		$H_3C–NH_2$			61
17					59
18					0

[a] Reaction conditions: phenacyl bromide (1.0 mmol), amine (1.0 mmol), diethyl or dimethyl acetylenedicarboxylate (1.0 mmol), PEG (5 mL), 60 °C.
[b] Isolated yields.

with aliphatic α-bromo ketone was not successful (Table 1, entry 18). The structures of all the products were determined from their analytical and spectral (IR, ^{1}H NMR and ^{13}C NMR) data[7] and by direct comparison with the authentic samples.

In conclusion, we have developed an efficient and facile method for the synthesis of polysubstituted pyrrole derivatives by treatment of phenacyl bromides, amine, and dialkyl acetylenedicarboxylate using PEG as a recyclable medium without the addition of any additive or organic co-solvent. The mild reaction conditions, less expensive of reaction medium, operational simplicity, and high yields are the advantages of the protocol.

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7. *General procedure for the synthesis of substituted pyrroles by using PEG as a reaction medium*: A mixture of the dialkylacetylene dicarboxylate (1.0 mmol), phenacyl bromide (1.0 mmol), and aniline (1.0 mmol) was taken in 5 ml of polyethylene glycol, and stirred at 60 °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.

Dimethyl 1,5-diphenyl-1H-pyrrole-2,3-dicarboxylate (Table 1, entry 2): ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.67–7.22 (m, 10H), 6.95 (s, 1H), 3.80 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 166.6, 160.1, 139.3, 133.1, 128.8, 128.4, 127.6, 127.0, 126.0, 125.8, 124.8, 123.1, 52.3, 51.8; mass (ESI): *m*/*z* 336 [M+1]; Anal Calcd for ($C_{20}H_{17}NO_4$): C, 71.63; H, 5.11; N, 4.18. Found: C, 71.57; H, 5.01; N, 4.11.

Diethyl 1,5-diphenyl-1H-pyrrole-2,3-dicarboxylate (Table 1, entry 3): ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.47–7.22 (m, 10H), 6.94 (s, 1H), 4.27 (dd, 2H, *J* = 6.79, 7.55 Hz) 4.13 (dd, 2H, *J* = 6.79, 7.55 Hz), 1.27 (t, 3H, *J* = 6.79 Hz), 1.16 (t, 3H, *J* = 6.79 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 166.1, 159.8, 139.5, 133.1, 128.7, 128.4, 127.6, 127.0, 126.1, 125.6, 124.6, 123.3, 121.9, 61.2, 60.7, 13.9, 13.8; mass (ESI): *m*/*z* 364 [M+1]; Anal Calcd for ($C_{22}H_{21}NO_4$): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.63; H, 5.76; N, 3.78.

Dimeth 5-(4-nitrophenyl)-1-phenyl-1H-pyrrole-2,3-dicarboxylate (Table 1, entry 6): ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 8.24 (d, 2H, *J* = 8.87 Hz), 7.59 (d, 2H, *J* = 8.87 Hz), 7.50–7.45 (m, 3H), 7.38–7.33 (m, 2H), 7.03 (s, 1H), 3.82 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ 166.2, 160.2, 146.9, 140.4, 139.1, 129.0, 128.8, 128.2, 126.0, 125.8, 124.9, 123.8, 122.8, 120.7, 52.4, 52.1; mass (ESI): *m*/*z* 381 [M+1]; Anal Calcd for ($C_{20}H_{16}N_2O_6$): C, 63.16; H, 4.24; N, 7.37. Found: C, 63.09; H, 4.18; N, 7.29.

Diethyl 5-(4-nitrophenyl)-1-phenyl-1H-pyrrole-2,3-dicarboxylate (Table 1, entry 7): ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 8.44 (d, 2H, *J* = 8.87 Hz), 7.83 (d, 2H, *J* = 8.87 Hz), 7.71–7.64 (m, 2H), 7.59–7.54 (m, 2H), 7.46 (s, 1H), 7.27 (s, 1H), 4.53 (dd, 2H, J = 7.98, 7.17 Hz) 4.36 (dd, 2H, *J* = 7.17 Hz), 1.50 (t, 3H, *J* = 6.98 Hz), 1.35 (t, 3H, *J* = 6.98 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ 165.4, 159.8, 146.7, 140.2, 139.0, 129.0, 128.8, 128.3, 126.0, 125.1, 123.8, 122.7, 122.4, 121.0, 61.5, 61.2, 14.0, 13.8; Mass (ESI): *m*/*z* 409 [M+1]; Anal Calcd for ($C_{22}H_{20}N_2O_6$): C, 64.70; H, 4.94; N, 6.86. Found: C, 64.62; H, 4.88; N, 6.79.

Diethy 5-(4-bromophenyl)-1-phenyl-1H-pyrrole-2,3-dicarboxylate (Table 1, entry 9): ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.52–7.39 (m, 5H), 7.36–7.25 (m, 4H), 6.91 (s, 1H), 4.25 (dd, 2H, *J* = 7.55, 6.79 Hz) 4.14 (dd, 2H, *J* = 7.55, 6.79 Hz), 1.29 (t, 3H, *J* = 6.79 Hz), 1.15 (t, 3H, *J* = 6.79 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 165.8, 159.9, 139.5, 132.3, 131.5, 130.8, 129.4, 128.9, 128.5, 126.1, 125.4, 124.2, 121.0, 61.3, 60.9, 14.0, 13.8; mass (ESI): *m*/*z* 442 [M+1]; Anal Calcd for ($C_{22}H_{20}BrNO_4$): C, 59.74; H, 4.56; N, 3.17. Found: C, 59.66; H, 4.59; N, 3.11.

Diethyl 1-ethyl-5-phenyl-1H-pyrrole-2,3-dicarboxylate (Table 1, entry 17): ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.59–7.05 (m, 5H), 6.85 (s, 1H), 4.49–3.98 (m, 6H), 1.67–0.99 (m, 9H): ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ 167.0, 160.1, 133.7, 128.4, 127.3, 126.7, 124.7, 123.4, 122.3, 120.3, 61.2, 60.5, 44.4, 16.9, 14.1, 14.0; mass (ESI): *m*/*z* 316 [M+1]; Anal Calcd for ($C_{18}H_{21}NO_4$): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.47; H, 6.65; N, 4.39.