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Polyethylene Glycol (PEG-400) as an Efficient and Recyclable Reaction Medium for One-Pot Synthesis of Substituted Pyrroles Under Catalyst-Free Conditions

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Polyethylene glycol (PEG-400) was found to be an effective and nontoxic reaction medium for the one-pot synthesis of substituted pyrroles under catalyst-free conditions in excellent yields. Environmental acceptability, low cost, high yields and recyclability of the polyethylene glycol are the important features of this protocol.

Keywords: Pyrroles, Aniline, Nitrostyrene, Acetyl acetone, Polyethylene glycol, Catalyst-free conditions.

INTRODUCTION

The pyrrole ring represents an important class of structural unit which is frequently found in many natural products[1], biologically and pharmaceutically active compounds[2,3]. It has been widely used as antitumor[4], antiinflammatory[5,6], antibacterial[7], antioxidant[8], and antifungal agents[9]. In addition, they are also useful in building blocks which are extensively used in material science[10,11]. The synthesis of pyrroles and their derivatives is usually achieved by well-known methods like Hantzsch[12,13] or Knorr[14], or Paal Knorr[15] reaction. The synthesis of tetra substituted pyrrole derivatives has been reported by Jana and co-workers by employing four-component reaction catalyzed by $FeCl_3$[16] or palladium mediated Suzuki reaction based on multicomponent reaction[17]. Menendez and his coworkers[18] reviewed the synthesis of pyrroles and their derivatives through multicomponent reactions (MCRs). 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 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, polyethylene glycol is inexpensive, easy to handle, thermally stable, nontoxic and recyclable for various organic transformations. To the best of our knowledge there are no previous reports on the synthesis of substituted pyrroles using polyethylene glycol-400 as a reaction medium under catalyst-free conditions. We report herein the synthesis of substituted pyrroles *via* tandem Michael addition-cyclization using PEG-400 as a recyclable medium without any additional organic solvent and catalyst.

EXPERIMENTAL

All the chemicals employed in this study were procured from Sigma Aldrich and Alfaesear. In present study, all the synthetic reactions were monitored by TLC and synthesized compounds were confirmed by various spectroscopic methods. The IR spectra were recorded using KBr pellets on a Perkin Elmer IR spectrophotometer. ^{1}H NMR spectra were recorded on Brucker 300 MHz Avance NMR spectrophotometer using $CdCl_3$ as solvent and TMS as internal standard (chemical shifts in d ppm). The mass spectra were recorded on Agilent 6300 series ion trap.

General procedure: The mixture of aniline (0.186 g, 2 mmol), nitrostyrene (0.149 g, 1 mmol), and acetyl acetone (0.120 g, 1.2 mmol) was taken in 5 mL polyethyleneglycol-400. The resulting mixture was allowed to stir at 85 °C for 8 h. After completion of the reaction, as monitored by TLC, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was removed under reduced pressure and the crude product was purified by column chromatography on silica gel using ethyl acetate: hexane mixture (3:7) as eluent to yield the desired product.

RESULTS AND DISCUSSION

We first attempted the reaction between simple aniline, nitrostyrene and acetyl acetone. The mixture of aniline, nitrostyrene and acetyl acetone was taken in 5 mL polyethylene glycol- 400. The resulting mixture was allowed to stir at 85 °C for 8 h. The progress of reaction was monitored by TLC, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was removed under reduced pressure and the crude product was purified by column chromatography on silica gel using ethyl acetate: hexane mixture (3:7) as eluent to yield 92 % of the desired product. (**Scheme-I**, entry-1 in Table-1).

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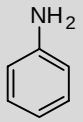
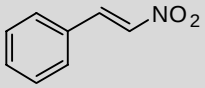
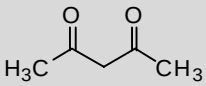
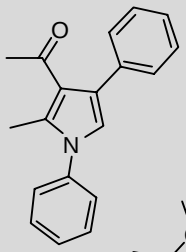
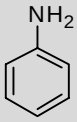
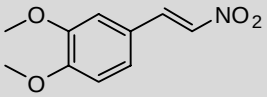
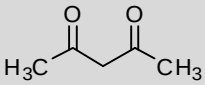
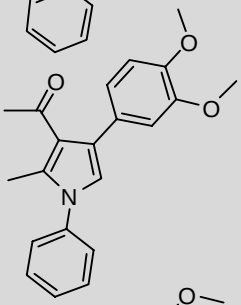
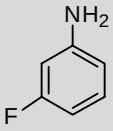
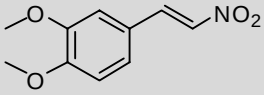
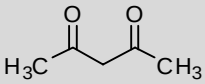
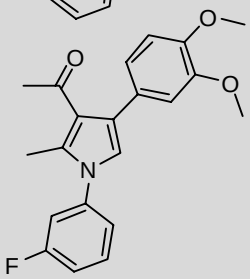
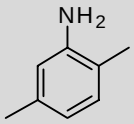
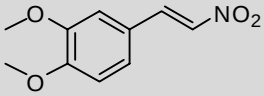
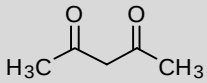
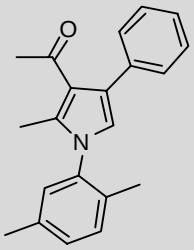
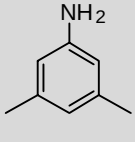
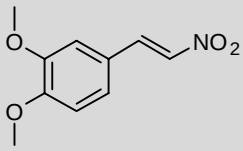
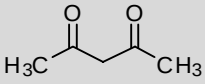
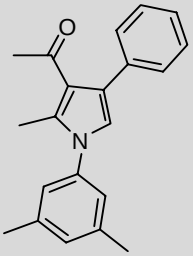
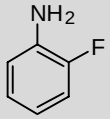
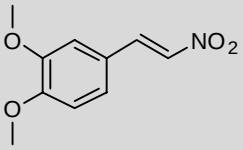
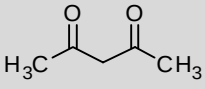
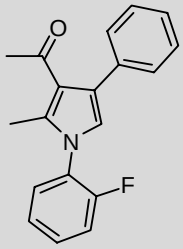
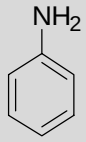
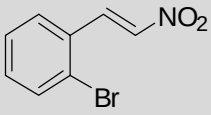
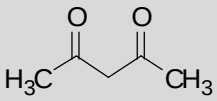
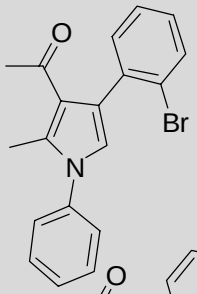
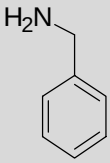
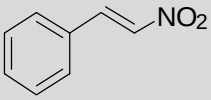
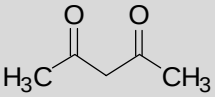
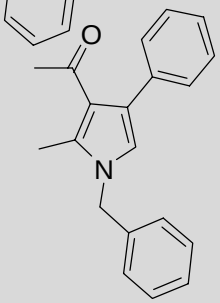
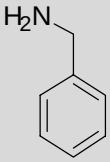
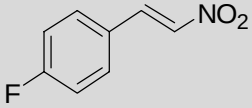
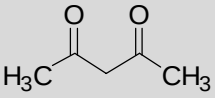
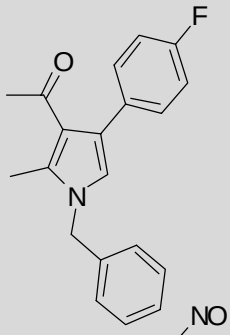
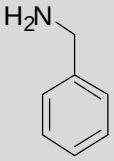
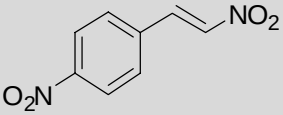
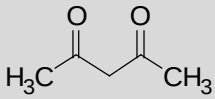
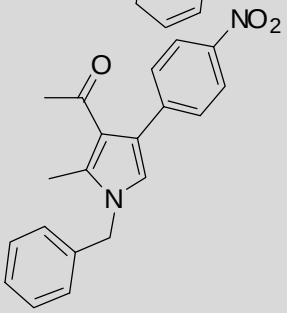
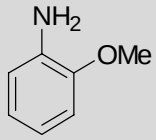
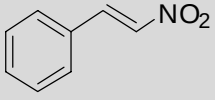
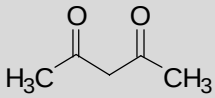
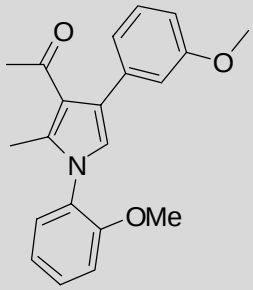
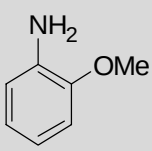
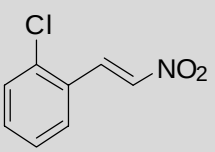
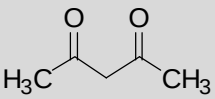
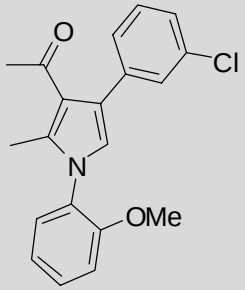
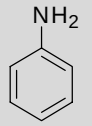
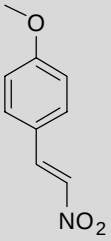
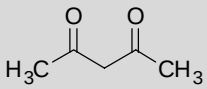
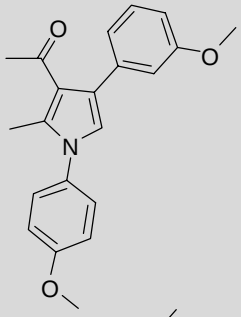
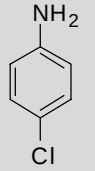
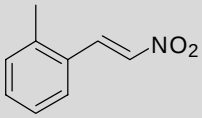
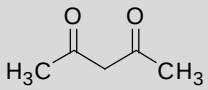
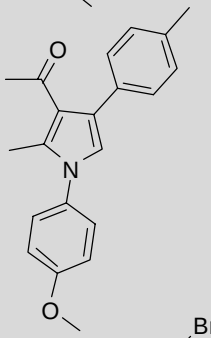
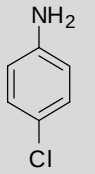
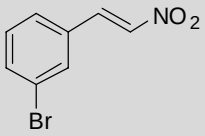
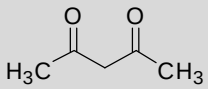
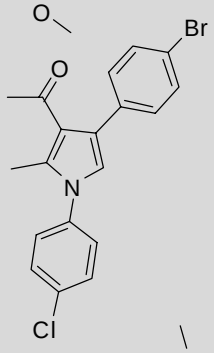
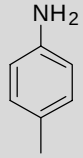
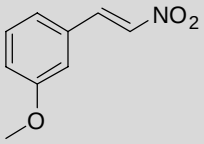
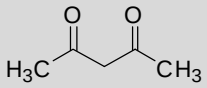
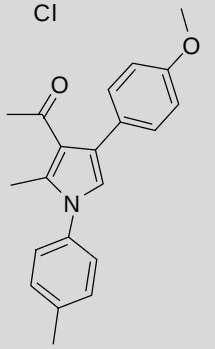
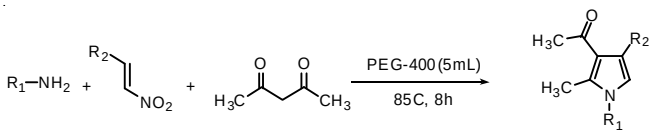
1					8	92
2					8	85
3					8	85
4					7	90
5					7	90
6					8	85

7					8	85
8					8	85
9					8	85
10					7	90
11					7	90
12					8	85

13					8	85
14					8	85
15					8	85
16					7	90

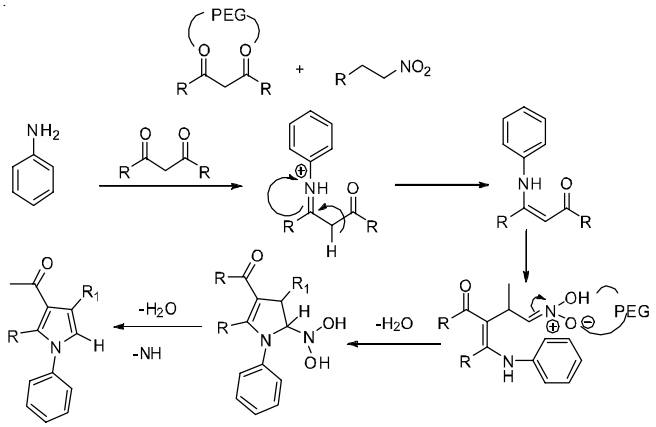


Scheme-I: PEG mediated synthesis of substituted pyrroles

The generality of this reaction was investigated by using wide variety of functionalized anilines and nitroolefines and the results are presented in Table-1.

The generality of solvent screening was done with the same example with variety of solvent medium and observed that the ethylene glycol is the best medium; results were mentioned in Table-2.

In general, all the reactions were very clean and the substituted pyrrole derivatives were obtained in high yields. anilines bearing electron-donating groups such as CH_3 and OCH_3, reacted efficiently (**Scheme-II**); whereas in the presence of



Scheme-II: A plausible reaction pathway

electron-withdrawing groups NO_2, a slight decrease in the yield of the substituted pyrroles was observed (Table-1 entries 6, 7,

TABLE-2
COMPARISON OF SOLVENTS IN THE SYNTHESIS OF PYRROLE

Entry	Solvent (5 mL)	Time (h)	Yield (%)
1	DMF	12	58
2	DMSO	10	60
3	NMP	10	57
4	Ethylene glycol	8	92

15 and 16). Aliphatic amines gave the desired products in low yields (Table-1, entries 9 and 18). The structures of all the products were determined from their analytical and spectroscopic (IR, ^{1}H NMR and ^{13}C NMR) data and also by direct comparison with authentic samples.

Conclusion

In conclusion, we have developed an efficient and facile method for the synthesis of substituted pyrrole derivatives from aniline, Nitrostyrene and acetyl acetone using polyethylene glycol as a recyclable medium without the addition of any additive or organic co-solvent. Mild reaction conditions, inexpensive reaction medium, operational simplicity and high yields are the advantages of this protocol.

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