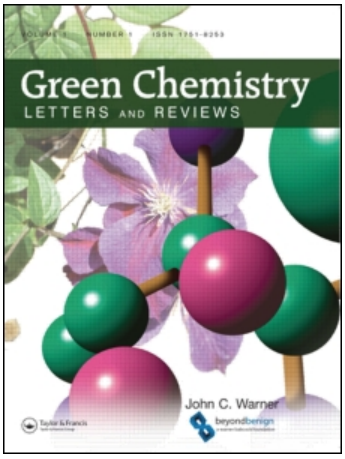

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RESEARCH ARTICLE

Polyethylene glycol (PEG) mediated green synthesis of 2,5-disubstituted 1,3,4-oxadiazoles catalyzed by ceric ammonium nitrate (CAN)

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Ceric ammonium nitrate in polyethylene glycol has been used as a sustainable, non-volatile, and ecofriendly catalytic medium for the green synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. This protocol is effective toward various substrates having different functionalities. The easy recyclability of the reaction medium makes the reaction economically and potentially viable for commercial applications.

Keywords: ceric ammonium nitrate; polyethylene glycol (PEG); 2,5-disubstituted 1,3,4-oxadiazoles; recyclability; ecofriendly

Introduction

1,3,4-Oxadiazoles are a class of heterocycles which have attracted significant interest in medicinal chemistry and they have a wide range of pharmaceutical and biological activities such as anti-inflammatory (*1*), anticonvulsant (*2*), and antibacterial activities (*3*). They have also shown antimitotic (*4*), antifungal (*5*), and muscle relaxant activity (*6*). In view of the great medical significance, a number of synthetic routes have been developed for 1,3,4-oxadiazoles (*7–9*). Many of these methods suffered from the drawbacks of strong acidic conditions, expensive reagents, long reaction times, harsh experimental conditions, and tedious work up procedures that generate large amounts of toxic waste. Hence the development of a synthetic protocol that is nature friendly, simple, efficient, and cost effective remains an ever challenging objective.

Recently, cerium (IV) ammonium nitrate has emerged as an important reagent for the construction of carbon–carbon and carbon–heteroatom bonds (*10,11*). In addition, many advantages such as excellent solubility in water, inexpensiveness, ecofriendly nature, easy handling, high reactivity, fast conversions, and convenient work up procedures make ceric ammonium nitrate (CAN) a potent catalyst in organic synthesis. Besides this, CAN is able to catalyze various organic transformations not only based on its electron transfer capacity, but also with its Lewis acidic property (*12–14*).

The conventional synthetic procedures invariably use organic solvents as media to provide a homogeneous phase that allows molecular interactions effectively and bring the reaction to completion. Regulatory pressure is increasingly focusing on the use, manufacture, and disposal of organic solvents and thus the development of non-hazardous alternatives (one of the several goals of green chemistry and engineering) is vitally important for the continued and sustainable development of the chemical enterprise. The use of water as a solvent is probably the most desirable approach but this is often not possible due to the hydrophobic nature of reactants. Therefore it was thought worthwhile to use polyethylene glycol (PEG) as the reaction media, as it may stand in comparison to other currently favored systems such as supercritical CO_2, near critical water, ionic liquids, and fluorous-based systems. Unlike these ''neoteric solvents'' whose environmental safety is still debated, complete toxicity profiles are available for a range of PEG molecular weights and indeed many are already approved for internal consumption by US FDA (*15*).

The versatility of CAN and the green nature of PEG encouraged us to couple them together and study their utility for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. In continuation of our studies on developing cheap and environmentally benign methodologies for organic reactions (*16,17*), we describe the use of a simple and widely available polymer, PEG as a non-toxic, inexpensive, and non-ionic liquid solvent of low volatility with CAN for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles **(3)** (Scheme 1).

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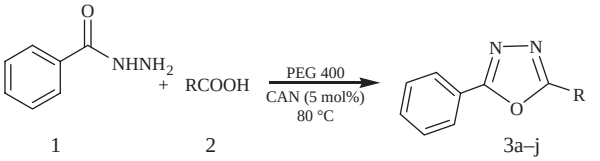

Scheme 1. Synthesis of 2,5-disubstituted oxadiazoles.

Results and discussions

In the beginning, efforts were made toward the catalytic evaluation of CAN toward the synthesis of oxadiazoles. The reaction using 1 equiv. of benzhydrazide **(1)** and 1 equiv. of carboxylic acid **(2a)** was performed in traditional organic solvent (EtOH, Figure 1). The reaction mixture was stirred for 32 h at 80°C to obtain 48% of oxadiazole **3a**. The same reaction was then carried out using PEG as the reaction medium under similar conditions. Surprisingly, a significant improvement was observed and the yield of **3a** dramatically increased to 83% after stirring the reaction mixture at 80°C for only 12 h. PEG as a reaction medium markedly catalyzed the reaction (Figure 1).

To further improve the yield and to optimize the reaction conditions, the same reaction was carried out in the presence of 2 mol% of CAN under similar conditions. A tremendous improvement was observed and the yield of **3a** was dramatically increased up to 94% after stirring the reaction mixture at 80°C only for 7 h. With this optimistic result in hand, we further investigated the best reaction conditions by using different amounts of CAN. An increase in the quantity of CAN from 2 to 5 mol% not only decreased the reaction time from 7 to 5 h, but also increased the product yield slightly from 94 to 98%. This showed that the catalyst concentration plays a major role in optimization of the product yield (Figure 2).

Various other Lewis acids were also tried for the reaction between 1 equiv. of benzhydrazide **(1)** and 1 equiv. of carboxylic acid **(2a)**, and it was found that CAN acted as the best catalyst for the synthesis of 2,5-disubstituted oxadiazoles (Table 1).

In order to prove that the use of PEG as a solvent is also practical, it must be conveniently recycled with minimal loss and decomposition. Since PEG is immiscible with solvent ether, the desired product may be extracted with it and the retained PEG phase may be reused. The reaction proceeded cleanly with consistent results for four runs, although a weight loss of approximately 5% of PEG was observed from cycle to cycle due to mechanical loss (Figure 3).

Based on the above observations, we conducted the same reactions using various carboxylic acids **(2a–j)** under similar conditions and as expected satisfactory results were observed (Table 2).

Experimental

All chemicals were purchased from Sigma–Aldrich and Lancaster, and were used as such. All reactions and purity of 2,5-disubstituted 1,3,4-oxadiazoles **(3)** were monitored by thin layer chromatography (TLC) using aluminium plates coated with silica gel (Merck) using 15% ethyl acetate, 5% methanol, and 80% petroleum ether as an eluent. The isolated products were further purified by column chromatography using silica gel (Sigma–Aldrich 24, 217–9,70, 35–70, mesh 40 Ao surface area 675 m^2/g) and purified product were

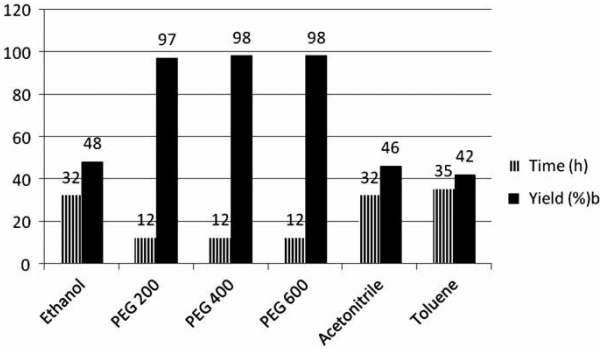

Figure 1. Synthesis of 2,5-disubstituted oxadiazoles in various solvents.[a]
[a]Reaction conditions: carboxylic acid (1 mmol), benzhydrazide (1 mmol); temperature 80°C; solvent.
[b]Isolated and unoptimized yields.

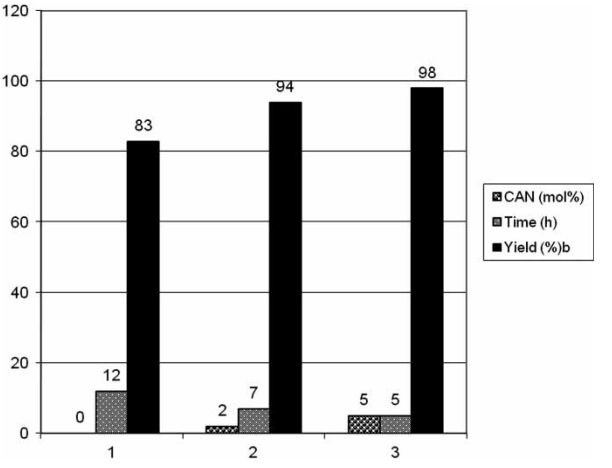

Figure 2. Catalytic activity evaluation of CAN for the synthesis of 2,5-disubstituted oxadiazoles.[a]
[a]Reaction conditions: carboxylic acid (1 mmol), benzhydrazide (1 mmol); temperature 80°C; PEG 400.
[b]Isolated and unoptimized yields.

Table 1. Screening of various Lewis acids for the synthesis of 2,5-disubstituted oxadiazoles.[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	$InCl_3$	11	87
2	CuO	8.5	79
3	$NbCl_5$	9	82
4	$FeCl_3$	9.5	73
5	I_2	7	76
6	$CuSO_4$	8	83
7	CAN	5	98

[a]Reaction conditions: carboxylic acid (1 mmol), benzhydrazide (1 mmol), catalyst (5 mol%); solvent PEG 400; temperature 80°C.
[b]Isolated and unoptimized yields.

recrystallized. IR spectra was recorded on a Perkin–Elmer FTIR-1710 spectrophotometer using Nujol film. ^{1}H NMR spectra was recorded on a Bruker Avance Spectrospin 300 (300 MHz) using TMS as an internal standard and chemical shift, in Δ. GC/MS mass spectra was recorded on a Waters LCT Micromass. The temperature of the reaction mixture was measured through a non-contact infrared thermometer (AZ, Mini Gun type, Model 8868).

General procedure for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

In a 50 ml round bottom flask, benzhydrazide (1 mmol) and carboxylic acid (1 mmol) in PEG 400 (0.2 ml) were mixed and stirred at 80°C. To this, CAN was added. The progress of reaction mixture was monitored by TLC. After completion of reaction, the reaction mixture was cooled in a dry ice-acetone bath to precipitate the PEG 400, and extracted with ether (PEG being insoluble in ether). Ether layer was decanted, dried, and concentrated under reduced pressure. The product, though seen as a single compound by TLC, was subjected to further purification by silica gel column chromatography using 15% ethyl acetate, 5% methanol, and 80% petroleum ether as an eluent to yield the product **3a**–**j**. The compounds were recrystallized using ethanol and chloroform by the layering technique. The recovered PEG 400 can be reused for consecutive runs. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, ^{1}H NMR, and GC/MS mass spectral data). All the products are known compounds.

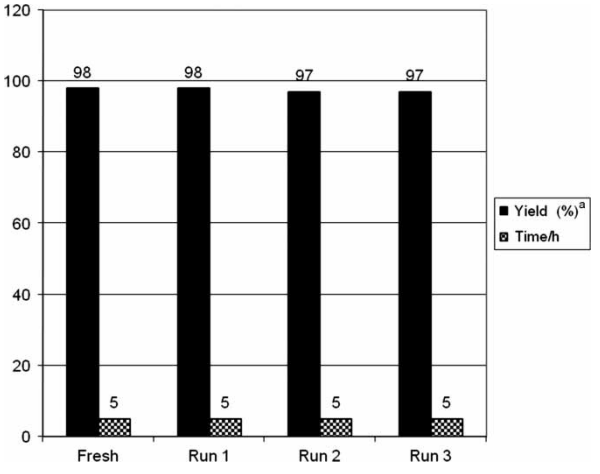

Figure 3. Recycling yields.
Note: Reaction conditions: carboxylic acid (1 mmol), benzhydrazide (1 mmol), CAN (5 mol%); solvent PEG 400; temperature 80°C.
[a]Isolated and unoptimized yields.

Spectral data of synthesized compounds

*2,5-Diphenyl-1,3,4-oxadiazole (**3a**, $C_{14}H_{10}N_2O$)*
ν max (KBr) cm^{-1} 3052, 2948, 1620, 1560, 1510, 1440, 1270, 1080, 1030, 710, 670; ^{1}H NMR (DMSO-d_6, TMS): Δ_H 7.52–7.57 (6H, m), 8.14–8.26 (4H, m); *m*/*z* (GC/MS, HRMS): 222.0797 (M^+, $C_{14}H_{10}N_2O$ required 222.0793). Analysis calculated for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.64; H, 4.53; N, 12.62.

*2-(2-Aminophenyl)-5-phenyl-1,3,4-oxadiazole (**3b**, $C_{14}H_{11}N_3O$)*
ν max (KBr) cm^{-1} 3450, 3350, 1630, 1590, 1450, 1272, 1120, 1045, 712, 678; ^{1}H NMR (DMSO-d_6, TMS): Δ_H 6.8–8.16 (9H, m, Ar), 11.2(2H, s, -NH_2); *m*/*z* (GC/MS, HRMS): 237.0908 (M^+, $C_{14}H_{11}N_3O$ required 237.0902). Analysis calculated for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.84; H, 4.66; N, 17.73.

*2-(2-Hydroxyphenyl)-5-phenyl-1,3,4-oxadiazole (**3c**, $C_{14}H_{10}N_2O_2$)*
ν max (KBr) cm^{-1} 3196, 2924, 1630, 1578, 1487, 1308, 1286, 1161, 1072, 1029, 708, 690; ^{1}H NMR (DMSO-d_6, TMS): Δ_H 7.12–8.18 (9H, m, Ar), 10.18 (1H, s, OH); *m*/*z* (GC/MS, HRMS): 238.0747 (M^+, $C_{14}H_{10}N_2O_2$ required 238.0742). Analysis calculated for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.59; H, 4.25; N, 11.78.

*2-(2-Methylphenyl)-5-phenyl-1,3,4-oxadiazole (**3d**, $C_{15}H_{12}N_2O$)*
ν max (KBr) cm^{-1} 3112, 2870, 1630, 1600, 1560, 1500, 1470, 1420, 1320, 1290, 1200, 1114, 1030, 840, 732, 700; ^{1}H NMR (DMSO-d_6, TMS): Δ_H 2.44

Table 2. Synthesis of various 2,5-disubstituted oxadiazoles.[a]

Entry	3	R	Time (h)	Yield (%)[b]	M.P (°C)	Lit M.P (°C)
1	**3a**	C_6H_5	5	98	132–133	132–133[18]
2	**3b**	2-$NH_2C_6H_5$	6	96	161–163	161–163[19]
3	**3c**	4-OHC_6H_5	6	91	165–166	165–166[20]
4	**3d**	4-$CH_3C_6H_5$	6	95	132–135	132–135[18]
5	**3e**	4-Cl C_6H_5	5	97	157–159	157–159[18]
6	**3f**	4-$OCH_3C_6H_5$	6	98	148–149	148–150[21]
7	**3g**	3-$OCH_3C_6H_5$	6	98	152–154	154–157[22]
8	**3h**	4-$NO_2C_6H_5$	5	95	200–203	200–204[23]
9	**3i**	Furyl	5	78	84–85	84–85[18]
10	**3j**	Pyridinyl	5	84	131–132	133–136[21]

[a]Reaction conditions: carboxylic acid (1 mmol), benzhydrazide (1 mmol), CAN (5 mol%); solvent PEG 400; temperature 80°C.
[b]Isolated and unoptimized yields.

(3H, s, CH_3), 7.32–7.56 (9H, m, Ar); *m/z* (GC/MS, HRMS): 236.0952 (M^+, $C_{15}H_{12}N_2O$ required 236.0950). Analysis calculated for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.22; H, 5.14; N, 11.87.

*2-(2-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (**3e**, $C_{14}H_9ClN_2O$)*

ν max (KBr) cm^{-1} 3100, 1620, 1570, 1510, 1422, 1321, 1280, 1100, 1082, 1030, 980, 840; ^1H NMR (DMSO-d_6, TMS): Δ_H 7.12–7.57 (9H, m, Ar); *m/z* (GC/MS, HRMS): 256.0408 (M^+, $C_{14}H_9ClN_2O$ required 256.0403). Analysis calculated for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91. Found: C, 65.53; H, 3.51; N, 10.92.

*2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (**3f**, $C_{15}H_{12}N_2O_2$)*

Mp ν max (KBr) cm^{-1} 3201, 1631, 1534, 1488, 1377, 1290, 1119, 1074, 1031, 931, 870, 706, 687; ^1H NMR (DMSO-d_6, TMS): Δ_H 3.86 (3H, s, -OCH_3), 6.97–7.43 (9H, m, Ar); *m/z* (GC/MS, HRMS): 252.0893 (M^+, $C_{15}H_{12}N_2O_2$ required 252.0899). Analysis calculated for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.40; H, 4.76; N, 11.12.

*2-(3-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (**3g**, $C_{15}H_{12}N_2O_2$)*

ν max (KBr) cm^{-1} 3119, 1632, 1532, 1445, 1377, 1288, 1102, 1078, 1030, 934, 878, 707, 687; ^1H NMR (DMSO-d_6, TMS): Δ_H 3.86 (3H, s, -OCH_3), 6.97–7.43 (9H, m, Ar); *m/z* (GC/MS, HRMS): 252.0896 (M^+, $C_{15}H_{12}N_2O_2$ required 252.0899). Analysis calculated for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.45; H, 4.78; N, 11.11.

*2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (**3h**, $C_{14}H_9N_3O_3$)*

ν max (KBr) cm^{-1} 3118, 2950, 1600, 1425, 1172, 1024, 940; ^1H NMR (DMSO-d_6, TMS): Δ_H 7.40–7.52 (5H, m), 8.21–8.52 (4H, m); *m/z* (GC/MS, HRMS): 267.0647 (M^+, $C_{14}H_9N_3O_3$ required 267.0644). Analysis calculated for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.72. Found: C, 62.94; H, 3.36; N, 15.76.

*2-(2-Furyl)-5-phenyl-1,3,4-oxadiazole (**3i**, $C_{12}H_8N_2O_2$)*

ν max (KBr) cm^{-1} 3150, 3120, 1630, 1562, 1544, 1500, 1467, 1350, 1180, 1139, 1100, 1080, 1052, 900; ^1H NMR (DMSO-d_6, TMS): Δ_H 6.64–6.67 (1H, m), 7.24 (1H, d), 7.35–7.55 (3H, m), 7.66–7.68 (1H, m), 8.12–8.14 (2H, m); *m/z* (GC/MS, HRMS): 212.0583 (M^+, $C_{12}H_8N_2O_2$ required 212.0586). Analysis calculated for $C_{12}H_8N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.46; H, 7.33; N, 12.74.

*2-(3-Pyridinyl)-5-phenyl-1,3,4-oxadiazole (**3j**, $C_{13}H_9N_3O$)*

ν max (KBr)/cm^{-1} 3118, 2950, 1601, 1423, 1172, 1025, 947; ^1H NMR (DMSO-d_6, TMS): Δ_H 7.51–7.59 (4H, m), 8.14–8.17 (2H, m), 8.45–8.48 (1H, m), 8.81 (1H, d), 9.37 (1H, s); *m/z* (GC/MS, HRMS): 223.0748 (M^+, $C_{13}H_9N_3O$ required 223.0746). Analysis calculated for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.92; H, 4.04; N, 18.81.

Conclusion

In conclusion, we have shown that CAN as a cheap and readily available catalyst is highly efficient for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. Moreover, PEG offers a convenient, inexpensive, non-ionic liquid, non-toxic, and recyclable reaction

medium for the synthesis of 2,5-disubstituted 1,3, 4-oxadiazoles. The recyclability of this catalyst system makes the reaction economically and potentially viable for commercial applications.

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