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Effect of Aqueous Polyethylene Glycol on 1,3-Dipolar Cycloaddition of Benzoylnitromethane/Ethyl 2-Nitroacetate with Dipolarophiles: Green Synthesis of Isoxazoles and Isoxazolines

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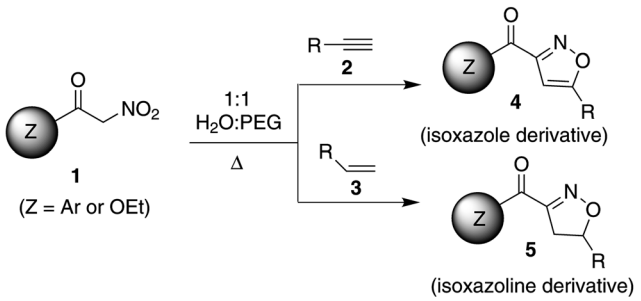
Abstract: A 1:1 mixture of water-polyethylene glycol (PEG) facilitated the 1,3-dipolar cycloaddition of benzoylnitromethane/ethyl 2-nitroacetate with terminal alkynes or alkenes leading to isoxazoles or isoxazolines under green conditions. The methodology is free from the use of any base, catalyst, dehydrating agent or hazardous solvent.

Keywords: cycloaddition; isoxazoles; isoxazolines; PEG; polyethylene glycol; water

The development of economic and eco-friendly methodologies that are free from the use of any catalyst, reagent, promoter or surfactant and are performed in aqueous media are the central focus of green and sustainable chemistry. Accordingly, we have devoted our efforts towards the construction of isoxazole and isoxazoline rings under clean reaction conditions.

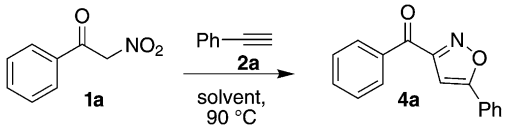
Isoxazoles are of considerable interest because of their versatile pharmacological properties.[1] They are also key building blocks for various complex molecules both in organic syntheses[2] and materials science.[3] Various methods have been reported for the synthesis of isoxazoles[4–8] including 1,3-dipolar cycloadditions where the primary nitro compounds (used as precursors of 1,3-dipoles) on cycloaddition with various dipolarophiles afforded isoxazoles and isoxazolines. Indeed, the activated nitro compounds after dehydration under acidic[9] or acylating conditions[10] or on severe heating[11] formed cycloadducts with dipolarophiles. These reactions can also be performed under milder conditions in the presence of ceric ammonium nitrate (CAN),[12] Boc_2O[13] or 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM).[14] The tertiary diamine (e.g., DABCO or TMEDA)-promoted, thermodynamically favoured dehydration of primary nitro compounds has also been reported by De Sarloa and Machetti et al.[15,16] The problem of the facile decomposition of the activated nitro compounds in the presence of water (generated *in situ*) and base was overcome by using a catalytic base.[17] In 2008, the same group reported the Cu/NMP-catalysed synthesis of 4,5-dihydroisoxazoles that avoided the use of anhydrous and inert atmospheres.[18] Later, Itoh et al. reported silica gel-supported polyphosphoric acid (PPA/SiO_2) as a reusable acid catalyst for the synthesis of 3-benzoylisoxazoles *via* the reaction of benzoylnitromethane with alkynes (dipolarophiles).[19] Despite being effective and efficient, many of these methods are either not economic or not eco-friendly. This and our continuing interest in greener approaches[20] towards various heterocyclic structures[21] prompted us to develop an alternative and catalyst-, reagent-, promoter- or surfactant-free synthesis of isoxazoles and isoxazolines. We now report the 1,3-dipolar cycloaddition of benzoylnitromethane/ethyl 2-nitroacetate (**1**) with dipolarophiles (**2**/**3**) in 1:1 H_2O:PEG 400 affording isoxazoles (**4**) and isoxazolines (**5**) (Scheme 1).

Initially, the reaction of benzoylnitromethane (**1a**) and phenylacetylene (**2a**) was examined in acetonitrile under reflux when no product was formed even after 20 h (entry 1, Table 1). Similar results were obtained in 1,4-dioxane (entry 2, Table 1), DMF (entry 3, Table 1) or DMSO (entry 4, Table 1). We then used PEG 400 (entry 5, Table 1) whereupon the desired isoxazole **4a** was isolated in 30% yield after 12 h. Notably, the reaction did not proceed in water (entry 6, Table 1) perhaps due to the poor solubility of the reactants in water. We then used a range of aqueous media, for example, water/1,4-dioxane



Scheme 1. Synthesis of isoxazole and isoxazoline derivatives.

Table 1. Optimization of the reaction conditions.[a]



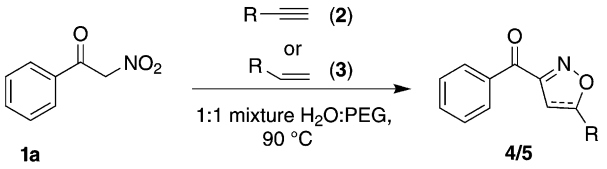
Entry	Solvent	Time [h]	Yield [%][b]
1	MeCN	20	0
2	1,4-dioxane	24	0
3	DMF	20	0
4	DMSO	20	0
5	PEG 400	12	30
6	H_2O	48	0
7	H_2O/1,4-dioxane (1:1)	12	0
8	H_2O/MeCN (1:1)	12	0
9	H_2O/DMF (1:1)	12	0
10	H_2O/DMSO (1:1)	12	0
11	H_2O/PEG-400 (1:1)	4	80
12	H_2O/PEG-400 (1:1)	6	88
13	H_2O/PEG-400 (1:1)	12	82
14	H_2O/EG[c] (1:1)	6	70
15	EG[c]	6	35

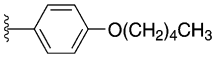
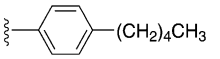
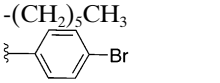
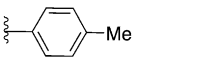
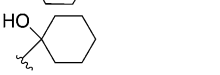
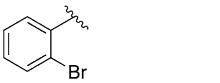
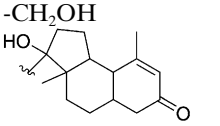
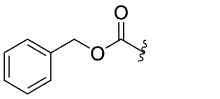
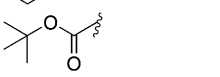
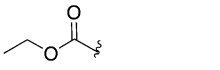
[a] Reactions were carried out using **1a** (1.0 mmol), phenylacetylene (**2a**) (1.0 mmol) and solvent (5 mL) at 90 °C.
[b] Isolated yield.
[c] EG = ethylene glycol.

(entry 7, Table 1), water/acetonitrile (entry 8, Table 1), water/DMF (entry 9, Table 1), water/DMSO (entry 10, Table 1) and water/PEG (entry 11, Table 1). However, the desired product **4a** was only obtained when a 1:1 mixture of water-PEG 400 was used. An increase in reaction time from 4 h to 6 h (entry 12, Table 1) or 12 h (entry 13, Table 1) did not improve the product yield significantly. Moreover, an attempt to perform the reaction at room temperature was not successful. To understand the role of the diol moiety of PEG 400, the same reaction was performed in water/ethylene glycol (1:1) whereby **4a** was obtained in 70% yield after 6 h (entry 14, Table 1). On the other hand, **4a** was isolated in only 35% yield when the reaction was performed in pure ethylene glycol (entry 15, Table 1). Overall, the conditions of entry 11 of Table 1 (i.e., heating at 90 °C in 1:1 water/PEG) were found to be optimum and used for further study.

To examine the generality and scope of this methodology various alkynes (**2**) as well as alkenes (**3**) were employed as dipolarophiles (Table 2). The reaction proceeded well with both aromatic (entries 1, 2, 3, 6, 7 and 9, Table 2) and aliphatic (entries 4, 5, 8, 10, 11, 12 and 13, Table 2) alkynes affording isoxazoles (**4**) in good yields. Isoxazoline derivatives (**5**) were obtained in moderate to good yields when alkenes (entries 14, 15, 16 and 17, Table 2) were used. We then examined the use of ethyl 2-nitroacetate (**1b**), 1-(4-chlorophenyl)-2-nitroethanone (**1c**) and 1-(4-

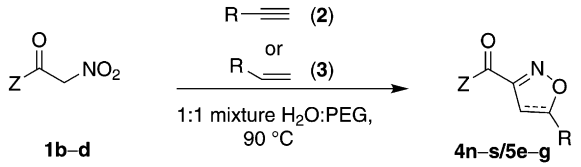
Table 2. Synthesis of isoxazoles (**4a–m**) and isoxazolines (**5a–d**).[a]

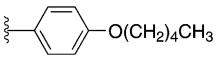
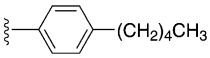
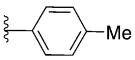
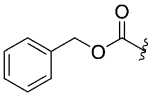
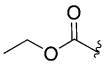


Entry	Terminal alkyne/alkene (**2**/**3**, R =)		Products	Time [h]	Yield[b] [%]
1	Ph	**2a**	**4a**	6	88
2		**2b**	**4b**	6	83
3		**2c**	**4c**	5	80
4	$-(CH_2)_4CH_3$	**2d**	**4d**	5	82
5	$-(CH_2)_5CH_3$	**2e**	**4e**	5	83
6		**2f**	**4f**	6	77
7		**2g**	**4g**	5	73
8		**2h**	**4h**	5	85
9		**2i**	**4i**	6	93
10	$-(CH_2)_4OH$	**2j**	**4j**	5	82
11	$-(CH_2)_3Cl$	**2k**	**4k**	5	79
12	$-CH_2OH$	**2l**	**4l**	5	80
13		**2m**	**4m**	6	71
14	Ph	**3a**	**5a**	6	46
15		**3b**	**5b**	5	93
16		**3c**	**5c**	5	82
17		**3d**	**5d**	5	80

[a] Reactions were carried out using **1a** (1.0 mmol) and **2** or **3** (1.0 mmol) in 1:1 H_2O-PEG-400 (5 mL) at 90 °C.
[b] Isolated yield.

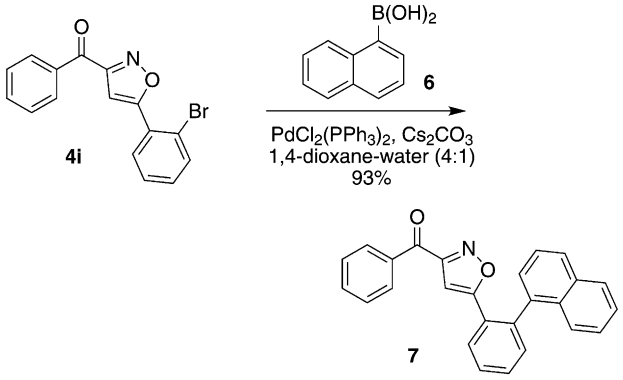
Table 3. Synthesis of isoxazoles (**4n–s**) and isoxazolines (**5e–g**).[a]



Entry	Z = (**1**)	Terminal alkyne/alkene (**2**/**3**, R =)		Products	Time [h]	Yield[b] [%]
1	EtO (**1b**)	Ph	**2a**	**4n**	6	80
2	(**1b**)		**2b**	**4o**	6	86
3	(**1b**)		**2c**	**4p**	5	84
4	(**1b**)		**2g**	**4q**	5	91
5	*p*-ClC_6H_4 (**1c**)		**2a**	**4r**	6	77
6	*p*-$MeOC_6H_4$ (**1d**)		**2a**	**4s**	6	74
7	(**1b**)	Ph	**3a**	**5e**	6	51
8	(**1b**)		**3b**	**5f**	5	81
9	(**1b**)		**3d**	**5g**	5	77

[a] Reactions were carried out using **1b–d** (1.0 mmol) and **2** or **3** (1.0 mmol) in 1:1 H_2O-PEG-400 (5 mL) at 90 °C.
[b] Isolated yield.

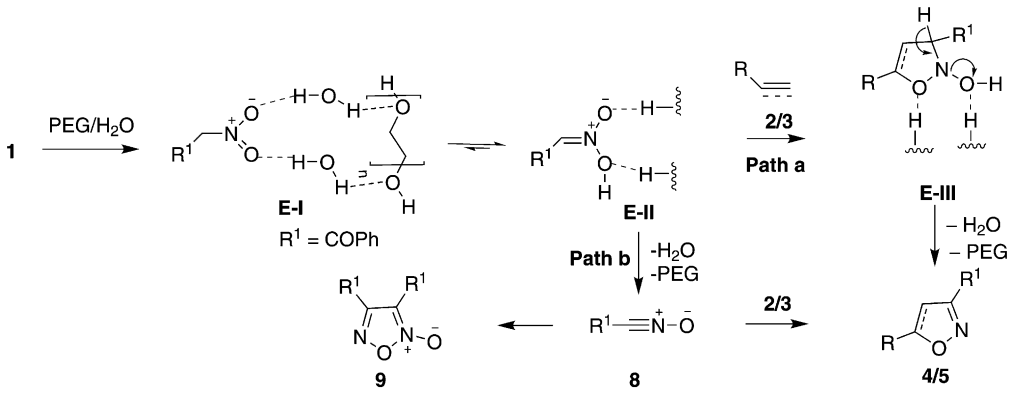
methoxyphenyl)-2-nitroethanone (**1d**) separately in place of **1a** (Table 3). Once again the reaction proceeded smoothly affording the corresponding products (e.g., **4n–s** and **5e–g**) in good yields. The recyclability of water-PEG mixture was examined by recovering (during work-up, see the Experimental Section) and reusing the solvent mixture twice in the reaction of **1a** with **2a** when **4a** was obtained in 83% and 80% yields after first and second cycle, respectively. All the compounds **4** and **5** synthesized were well characterized by NMR, IR, MS and HR-MS spectral data. The =CH− moiety of the isoxazole ring appeared at $\delta = 6.5$–7.0 (singlet) and $\delta = 99$–100 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. The benzoyl/ester carbonyl appeared at $\delta = 185.8/171.5$ ppm in the ^{13}C NMR and at 1662/1725 cm^{-1} in the IR spectra. Similarly, the $-CH_2-$ moiety of the isoxazoline ring appeared as a double doublet near $\delta = 3.63$ and 3.55 (^{1}H NMR) and $\delta = 37$–38 ppm (^{13}C NMR) while the −CH− moiety appeared at $\delta = 5.10$ (double doublet, ^{1}H NMR) and 79-84 ppm (^{13}C NMR). To expand the scope of the present methodology, further the structural elaboration of a representative isoxazole **4i** was performed *via* Suzuki coupling with the boronic acid **6** (Scheme 2).



Scheme 2. Structural elaboration of **4i** *via* Suzuki coupling.

Based on the fact that PEG/H_2O played a key role in the present reaction (Table 1) a plausible mechanism[7,22] involving the activation of the nitro group aided by PEG/H_2O is shown in Scheme 3. Thus a chelate type of complex **E-I**, formed *via* H-bonding[23] between **1** and PEG-H_2O was tautomerized to **E-II** that underwent 1,3-dipolar cycloaddition with **2** or **3** (path a, Scheme 3) to form **E-III**, which on elimination of water and PEG afforded the product **4** or **5**. While the formation of **4/5** *via* generation of nitrile oxide **8** (path b, Scheme 3) followed by its cycloaddition with **2/3** cannot be ruled out, the dimerization of **8** to furoxan **9** (in absence or presence of dipolarophiles) was often found to be a side reaction in such a case.[15,20] Since the formation of **9** was not detected[24] in the present case the reaction perhaps did follow the path a.

In conclusion, the present research demonstrates the first use of aqueous PEG-400 in facilitating the 1,3-dipolar cycloaddition of benzoylnitromethane/



Scheme 3. Proposed reaction mechanism.

ethyl 2-nitroacetate with terminal alkynes or alkenes leading to isoxazoles or isoxazolines under green conditions. The methodology is free from the use of any base, catalyst, dehydrating agent or hazardous solvent and is amenable for the synthesis of complex molecules.

Experimental Section

General Procedure for the Synthesis of Isoxazole (4)/ Isoxazoline (5) Derivatives

A mixture of benzoylnitromethane/ethyl 2-nitroacetate (**1**) (1.0 mmol) and alkyne (**2**)/alkene (**3**) (1.0 mmol), in water (2.5 mL) and polyethylene glycol (PEG-400) (2.5 mL) was stirred at 90 °C for 4–6 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and extracted with EtOAc (2 × 10 mL). The EtOAc layers were collected, combined, washed with cold water (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under low pressure. The residue was then purified by column chromatography (petroleum ether-EtOAc) affording the desired isoxazole (**4**)/ isoxazoline (**5**) derivatives.

Recovery of Aqueous PEG

The aqueous layer containing water and PEG was collected after work-up and the contaminated EtOAc was removed *via* distillation. The mixture was recycled for two times without significant loss of product yield (see the text).

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