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Brønsted acid-catalyzed simple and efficient synthesis of 1,2,4-triazoles and 1,2,4-oxadiazoles using 2,2,2-trichloroethyl imidates in PEG

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ABSTRACT

A facile and highly efficient synthesis of 3,4,5-trisubstituted 1,2,4-triazoles and 3,5-disubstituted 1,2,4-oxadiazoles from 2,2,2-trichloroethyl imidates using PEG as a solvent and employing PTSA as the catalyst under mild conditions is described.

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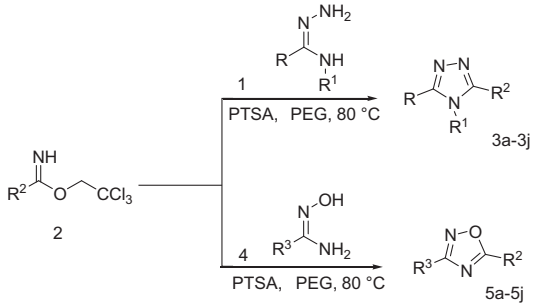
The study of heterocyclic systems such as triazoles and oxadiazoles is known to have considerable development due to their varied effects in diverse domains. In general, 1,2,4-triazoles and 1,2,4-oxadiazoles have been attracting attention over the last decade due to their biological activities such as anti-inflammatory,[1] antibacterial,[2] antitumor,[3] and antiviral.[4] In the view of greater medical significance, a number of synthetic routes have been developed for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles and 3,5-disubstituted 1,2,4-oxadiazoles. Generally, synthesis of these heterocyclic compounds is carried out by a two-step method. Initially carboxylic acids couple with amidrazones or amidoximes followed by cyclodehydration in the next step to afford corresponding 1,2,4-triazoles[5] or 1,2,4-oxadiazoles,[6] respectively. Moreover, these heterocyclic compounds were also synthesized in one pot directly from corresponding amidrazones and amidoximes using anhydrides.[7] However, these protocols suffered from the limitation of harsh conditions, tedious synthetic procedures, and unsatisfactory yields. Therefore, developing a mild and more general procedure to access 1,2,4-triazoles and 1,2,4-oxadiazoles is still highly desirable.

Imidates[8] are easily prepared by reaction of a nitrile and ethanol in the presence of HCl. These compounds have been used as reagents for the preparation of *s*-triazines, diazirines, selenoesters, selenoamides, and 2-substituted pyrimidine-4-(3*H*)-ones, and also conversion of pyrimidine into pyridine. Depending on the nature of the amine nucleophile, the imidates can react either as the free-base or the hydrochloride salt. Based on their successful use as electrophiles, we considered additional applications for these reagents and recognized that nitrogen could serve as a second leaving group in the form of protonated ammonia under acidic conditions.

Recently, polyethylene glycol (PEG) is found to be an interesting eco-friendly solvent system in synthetic organic chemistry[9] with unique properties such as nontoxic, inexpensive, and nonionic



Scheme 1. Preparation of 3,4,5-trisubstituted 1,2,4-triazoles and 3,5-disubstituted 1,2,4-oxadiazoles.

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liquid solvent of low volatility. PEG is a biologically acceptable polymer which has been used extensively in drug delivery and in bioconjugates as tools for diagnostics.[10]

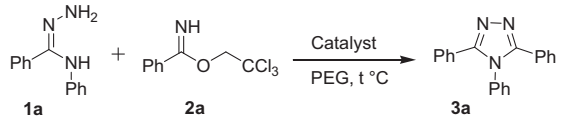
In continuation of our studies[11] in developing inexpensive and environmentally benign methodologies for the synthesis of bioactive molecules, herein, we report a novel and direct synthesis of 3,4,5-trisubstituted 1,2,4-triazoles and 3,5-disubstituted 1,2,4-oxadiazoles from 2,2,2-trichloroethyl imidates using PEG as a solvent and employing PTSA as the catalyst (Scheme 1).

In order to investigate the reaction conditions for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles, we have chosen the reaction of amidrazone, 2,2,2-trichloroethyl imidate in PEG as a model reaction. Thus, amidrazone (**1a**) (1.7 mmol) was treated with 2,2,2-trichloroethyl imidate (**2a**) (1.8 mmol) in PEG (5 mL) at 80 °C without any catalyst. The product was obtained in very low yield after prolonged time. Therefore, our efforts were focused on the search for a suitable catalyst. Initially, acetic acid (20 mol %) was chosen as a catalyst to carry out this reaction. As a result, long reaction times with poor yields were observed. Use of trifluoroacetic acid (20 mol %) as a catalyst gave satisfactory yield (Table 1, entry 2). Encouraged by these results, we turned our attention to various Brønsted acids; these were screened in our model reaction (Table 1). Finally, we found that PTSA showed high catalytic activity in terms of reaction time as well as yield of the product. The effect of amount of catalyst on the conversion and rate of the reaction was studied by varying the amount of PTSA using PEG as solvent (Table 1). It was found that 40 mol % of PTSA was sufficient to carry out this reaction smoothly (Table 1, entry7). The effect of temperature on reaction rate as well as on yields of products was also investigated. Faster reactions occurred on increasing the temperature but the product yields were not satisfactory (Table 1, entries 9 and 10). Progress of the reaction was monitored by TLC analysis (using EtOAc/hexane as eluents).

Further, we screened a variety of solvents, and examined their effect on reaction times and yields (Table 2). Thus, aprotic solvents like toluene, dioxane gave no positive effects, whereas protic solvents like isopropyl alcohol (IPA) or polyethylene glycol (PEG) improved the yield and declined the reaction time. However, PEG had superior solvent effects for this reaction and was therefore used for all subsequent reactions (Table 2, entries 6–8).

To explore the generality and scope of the method, the optimized reaction conditions (amidrazone (1) (1.7 mmol), 2,2,2-trichloroethyl imidate (2) (1.8 mmol), PEG (5 mL), and PTSA (40 mol %) at 80 °C) were applied to various structurally diverse amidrazones and 2,2,2-trichloroethyl imidates (Table 3). From the results detailed in Table 3, we can discern that this reaction tolerates a wide scope of amidrazone derivatives with either electron-donating or electron-withdrawing substituents on the aryl residue and 2,2,2-trichloroethyl imidates with aryl or alkyl substituents.

Table 1
Effect of various catalysts in the synthesis of **3a**



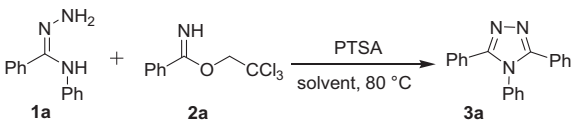
1a **2a** **3a**

Entry	Catalyst (mol %)	Temp (°C)	Time (min)	Yield[a] (%)
1	AA (20)	80	32	36
2	TFA (20)	80	28	56
3	BSA (20)	80	25	59
4	Sulphanilic acid (20)	80	22	61
5	PTSA (20)	80	18	86
6	PTSA (30)	80	11	86
7	PTSA (40)	80	9	86
8	PTSA (50)	80	9	86
9	PTSA (40)	100	7	52
10	PTSA (40)	120	7	46

AA-acetic acid, TFA-trifluoroacetic acid, BSA-benzene sulfonic acid, PTSA *p*-toluene sulfonic acid.

[a] Isolated yield after column chromatography.

Table 2
Effect of various solvents in the synthesis of **3a**

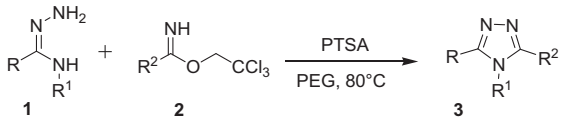


1a **2a** **3a**

Entry	Solvent	Time (min)	Yield[a] (%)
1	Toluene	21	58
2	1,4-Dioxane	22	61
3	Acetonitrile	22	60
4	IPA	23	76
5	PEG 200	9	86
6	PEG 300	9	86
7	PEG 400	9	86

[a] Isolated yield after column chromatography.

Table 3
Synthesis of various 3,4,5-trisubstituted 1,2,4-triazoles from the corresponding amidrazones and 2,2,2-trichloroethyl imidates[12]

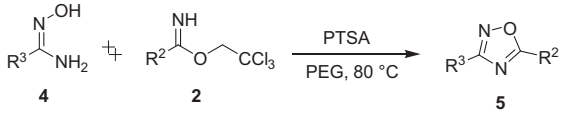


1 **2** **3**

Entry	R	R^1	R^2	Product	Yield[a] (%)
1	Ph	Ph	Ph	**3a**	86
2	Ph	4-BrPh	Ph	**3b**	84
3	Ph	3-ClPh	Ph	**3c**	86
4	Ph	3-ClPh	4-MePh	**3d**	85
5	Ph	Ph	4-OMePh	**3e**	88
6	Ph	4-BrPh	4-OMePh	**3f**	86
7	Ph	4-MePh	4-OMePh	**3g**	88
8	Ph	4-BrPh	4-ClPh	**3h**	83
9	Ph	4-ClPh	Et	**3i**	81
10	Ph	Ph	Cyclohexyl	**3j**	80

[a] Isolated yield after column chromatography.

Table 4
Synthesis of various 3,5-disubstituted 1,2,4-oxadiazoles from the corresponding amidoximes and 2,2,2-trichloroethyl imidates[12]



4 **2** **5**

Entry	R^3	R^2	Product	Yield[a] (%)
1	Ph	Ph	**5a**	92
2	Ph	4-MePh	**5b**	91
3	4-Me Ph	4-MePh	**5c**	91
4	Ph	4-ClPh	**5d**	89
5	2-Py	Ph	**5e**	91
6	2-Py	2-Py	**5f**	89
7	Ph	Me	**5g**	92
8	Ph	Et	**5h**	90
9	2-Py	Et	**5i**	92
10	Ph	Cyclohexyl	**5j**	89

[a] Isolated yield after column chromatography.

The above results motivated us to look for a simple method for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles. Fortunately, following the above protocol, we were able to prepare 3,5-disubstituted 1,2,4-oxadiazoles very efficiently using amidoximes and 2,2,2-trichloroethyl imidates. This method was found to be quite general (amidoxime (4) (1.7 mmol), 2,2,2-trichloroethyl imidate (2) (1.8 mmol), PEG (5 mL), and PTSA (40 mol %) at 80 °C) and worked well for a variety of aromatic and hetero aromatic amidoximes, as well as alkyl and aryl substituted 2,2,2-trichloroethyl imidates (Table 4).

In conclusion, we have developed a simple, efficient, and eco-friendly convenient general method for the synthesis of 1,2,4-triazoles and 1,2,4-oxadiazoles from 2,2,2-trichloroethyl imidates using PEG as a solvent and employing PTSA as the catalyst under mild conditions. This method provided structurally diverse 1,2,4-triazoles and 1,2,4-oxadiazoles in excellent yields. 1,2,4-triazoles and 1,2,4-oxadiazoles derivatives are biologically and pharmaceutically active molecules, and therefore, the present protocol could be of wide application in medicinal chemistry and organic chemistry.

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Supplementary data

Supplementary data associated (general experimental procedure and spectral analysis data) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.147.

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12. *General experimental procedure for the synthesis of **3** and **5**:* A mixture of 2,2,2-trichloroethyl imidate (1.8 mmol), amidrazone (1.7 mmol) or amidoxime (1.7 mmol), PEG-400 (5 mL), and PTSA (1.0 mmol) was heated to 80 °C for 9 min. After completion of the reaction as monitored by TLC, reaction mixture was cooled to room temperature, aqueous Na_2CO_3 solution (10 mL) was added and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield **3** or **5** which was purified by silica gel column chromatography using EtOAc/hexane (5:5) as eluents.
*3,4,5-Triphenyl-4H-1,2,4-triazole (**3a**):* Mp: 287–289 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 6H). 7.30–7.19 (m, 7H), 7.06–7.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 135.2, 129.9, 129.5, 128.8, 128.8, 128.3, 127.8, 126.9; LCMS: m/z = 298 $[M+1]^+$. Anal. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13. Found: C, 80.72; H, 5.11; N, 14.11.
*3,5-Diphenyl-1,2,4-oxadiazole (**5a**):* Mp: 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.56 (m, 6H), 8.18–8.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.3, 127.0, 127.5, 128.1, 128.8, 129.0, 131.1, 132.6, 168.9, 175.7; LCMS: m/z = 223 $[M+1]^+$. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.71; H, 4.56; N, 12.52.