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On-water, Catalyst-Free and Room-temperature Construction of 2-Aryl-1,3,4-oxadiazole Derivatives from 1,1-Dichloro-2-nitroethene and Hydrazides

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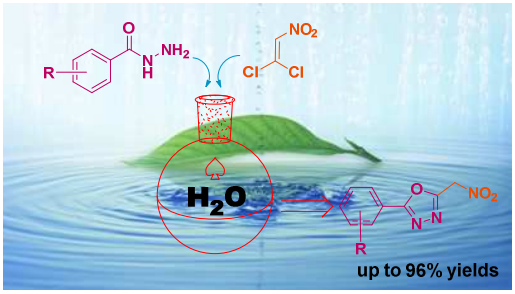
Table of contents entry



The image of Construction of 2-Aryl-1,3,4-oxadiazole Derivatives from 1,1-Dichloro-2-nitroethene and Hydrazides

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Abstract: 2-Aryl-1,3,4-oxadiazoles are important functional molecules in many research fields. A green synthetic method for preparation of 2-aryl-1,3,4-oxadiazoles was developed using hydrazides and highly reactive 1,1-dichloro-2-nitroethene. This eco-friendly protocol featured by high yields, purification simplicity, water-based reaction medium, energy efficiency and no addition of catalysts.

Introduction

The greening of synthetic methods has become one of the most important research topics in organic chemistry in recent decades owing to the stringent concerns on environmental protection, sustainable development and energy crisis.[1] One of the twelve principles[2] in green chemistry is using safer solvents. Water meets the needs for an ideal solvent due to its fascinating properties such as abundance, easy availability, high heat capacity, non-toxicity, nonflammability and redox stability.[3] In addition, driving the reaction in void of catalysts is also long pursued by chemists to fulfill the goal of greening. Thus, there is much interest in developing in-water / on-water[4,5] or catalyst-free synthetic methods with high efficiency, low-energy consumption and easy operation.

Aryl-1,3,4-oxadiazoles (AODAs) are frequently-appeared intermediates or structural fragments in organic and medicinal chemistry as well as in polymer and material science.[6-8] Simply searching the AODA as substructure in Scifinder, more than 120,000 results are presented relating to its preparation as intermediates or final products. This high degree of concerns is attributed to their involvement in a variety of biological compounds across many areas ranging from pharmaceuticals to pesticides,[9,10] such as cancer,[7,11,12] diabetes,[13] obesity,[14] infection,[15-18] insecticides,[19] and herbicides.[20-22] Raltegravir,[23] Tiodazosin,[8] Nosapidil[8,24] and Furamizole[8,24] are oxadiazole derivatives already presented in the market. Furthermore, this functionality has also been served as surrogates of carbonyl containing compounds including carboxylic acid, esters amides, carbamates and hydroxamic esters.[25-27]

In light of their importance, a number of different strategies have been developed for the construction of AODAs. The most commonly used building blocks are hydrazides, which underwent cyclization by phosphorus oxychloride,[28,29] 2-chloroacetic acid,[30,31] thionyl chloride,[32] cyanic bromide[33] and Burgess reagent.[34] Milder reaction conditions were accomplished by employing of phosphonium, dimethylimidazolinium chloride, PPh_3 and bistriphenylphosphonium ditriflate (P^V-reagent).[35] In recent years, some notable improvement to synthesize this heterocycle scaffold can be summed up as cyclization of hydrazide with orthoformates catalyzed by

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ammonium chloride,[36] Nafion catalyzed synthesis under microwave[37] and sonochemical synthesis from benzoic acid.[38] However, most strategies suffered from one or more drawbacks which do not fit the role of green chemistry, such as use of organic solvents and expensive catalysts, high temperature, long reaction time, low yields, microwave irradiation and ultrasound acceleration. Therefore, an urgent need exists to search for a versatile methodology for preparing AODAs in a greener manner. Herein, we presented a novel way utilizing 1,1-dichloro-2-nitroethene (DCNE) as building blocks to efficiently synthesize AODAs. The reaction is characterized by on-water, catalyst-free, high yields and easy operation and purification.

Results and Discussion

DCNE is a reactive chemical intermediate, the strong electro-withdrawing nitro makes the C=C double bond highly polarized. The high polarized structure was confirmed on the basis of analysis of electrophilicities of nitrothene.[39-41] The calculation studies indicated that the electronic density around the β-carbon is lower than that in 1,2-dichloroethylene, almost the same level with that in phosgene (Fig. 1). Thus, the α-carbon and the β-one can be easily attacked by nucleophiles and electrophiles, respectively. When the reaction behavior of DCNE with hydrazides were explored, we happily to found that the reaction proceeded smoothly affording AODA **5a** with high efficiency (Scheme 1).

We began by examining the model reaction of benzohydrazide (BHA) **4a** with DCNE. The solvents were firstly screened (Table 1). In this typical reaction, simple mixing of the two reactants in various organic solvents at room temperature without catalysts gave the oxadiazole products **5a** instead of the three-membered **6**. Furthermore, the structure of **5a** was identified by X-Ray diffraction studies[42] (Fig. 2). However, the yields were relatively low (20-60%) even the reaction time was prolonged to 96 hours. No significant correlation of yields with solvent polarity was observed. Toluene gave the highest yields reaching up to 58%. While in ethanol and methanol the yields were quite low (around 20%). In order to fasten the reaction, the temperature-yields effect was then evaluated in toluene. Elevating the reaction temperature had dual effects, high yields (95%) and reaction rates (2 h). Upon further investigation, we happily found that the reaction proceeded very well when water was used as the reaction medium, with almost the quantitative conversion (more than 90%). Moreover, the product precipitated from the reaction mixture and can be easily separated by filtrate with good purity (97%). The acid capturer is unnecessary to the high conversion, although two equivalent of hydrochloride acid generated during the reaction. The reaction proceeded more rapidly at 50 °C furnishing the corresponding AODA in excellent yields, but for energy-saving consideration, this condition was not used for further scopes study. Making it together, the advantages of using water as solvent are catalyst-free, no side reaction, easy operation and purification and energy saving. Such a green strategy may provide alternative for AODAs preparation. The success of using water as solvent might be due to the low solubility of DCNE in water, which reduces its reactivity. Furthermore, the product precipitated from the reaction mixture, which further drives this conversion.

Having the intriguing results above, the scope of this methodology was further explored (Table 2). In all cases, quantitative formation of AODAs was achieved upon simply stirring the reaction mixture of DCNE and BHAs on water at room temperature. The structures of the AODAs were

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well characterized by ^{1}H NMR, ^{13}C NMR and HRMS study. A variety of functional groups such as nitro, methyl, methoxy as well as halogens were all compatible with this transformation. Notably, the *para*-substituted (5d, 5g, 5i, 5l) BHAs also gave high yields, which was previously difficult to be obtained in desired yields. The electron features or substituted-positions of the substituents in BHAs had little influence on the efficiency of this protocol. Overall, the electron-donating substituents have favorable effects to the reaction, but the difference was not obvious compared with the electron-withdrawing ones. For the trimethoxy-substituted (5m) BHA, the yields were relatively low probably due to the electron effects of three methoxy substituents.

For many substrates or groups are sensitive to water through degradation and hydrolysis, the feasibility and high efficiency of this reaction were also verified in the organic solvents, fortunately, the reaction proceeded well in the toluene with almost the same yields obtained on water.

The change of the aromatic unit of BHA with heterocyclic one (Table 2, entry 14, 5n) did not influence reactivity with a bit lower yields (85%), We were also pleased to find that the reaction system could be successfully applied to *iso*- and *tere*-phthalic dihydrazides (Table 2, entry 15 and 16, 5o, 5p, respectively) with high yields and purity. However, in case of dihydrazide substituted at the *ortho*-position (Table 3, entry 3), the phthalhydrazide was formed instead of corresponding AODA due to the instability and easy cyclization of this kind of dihydrazide.

Reaction of the alkyl hydrazide (Table 3, entry 1) was unsuccessful with the complexation of the reaction. Reaction of heterocyclic hydrazide thiophene-2-carbohydrazide proceeded well with high yields. This phenomenon was also proved by other types of base such as TEA, DIPEA and pyridine with the formation of brown or red salts.

Then we investigated the more complex hydrazides, such as phenyl-substituted hydrazide (Table 3, entry 4 and 5) and cyclic hydrazide (Table 3, entry 6), unfortunately, nitro acetylation of the compound was observed. The possible formation of nitro acetyl-products were depicted in Scheme 2. In this proposed pathway, the cyclized intermediate C was formed followed by the hydrolysis of the cycle due to the instability. This observation suggested that the primary amine moiety is essential to the formation of AODA. Cyclic substrate 2-aminoisoindoline-1,3-dione was also explored affording the unseparated products (Table 3, entry 7).

In order to elucidate reaction pathways, the ^{1}HNMR tracking of the model reaction in D_2O was studied. ^{1}HNMR spectra in D_2O collected during the course of the reaction only revealed the consumption of BHA (Fig. 4). The increase of H_2O peak at δ 4.74 indicated that the formation of hydrogen chloride. This observation suggested that the formation of AODA occurred immediately and no other intermediates formed during the process. Based on the observation from the current study, a plausible reaction pathway was proposed (Scheme 2). The reaction was initiated by the nucleophilic substitution of BHA to DCNE to give intermediate A which underwent tautomerization affording B. The subsequent intramolecular nucleophilic attack occurred giving intermediate C which tautomerized to final product.

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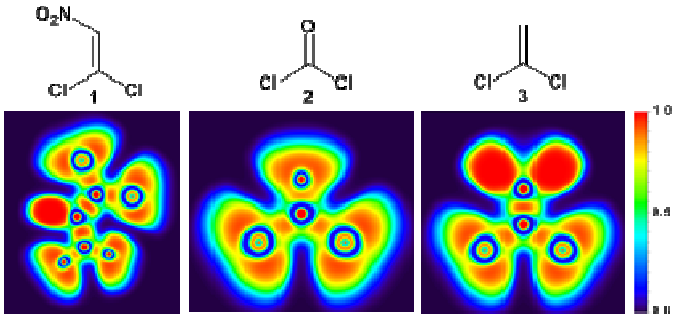
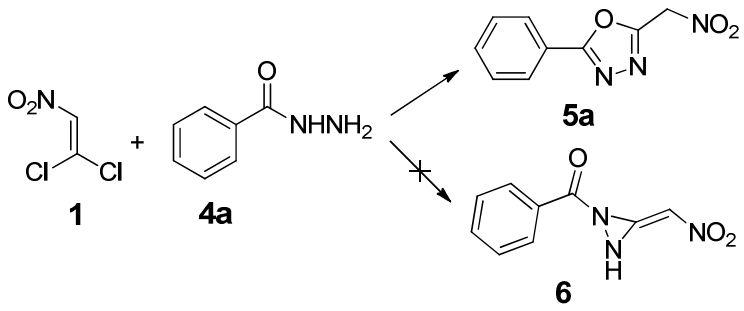


Fig. 1. Chemical structure of DCNE, phosgene and 1,1-dichloroethene and their electron density maps (electrostatic potential maps)



Scheme 1. Reaction of DCNE with benzohydrazide, a possible product

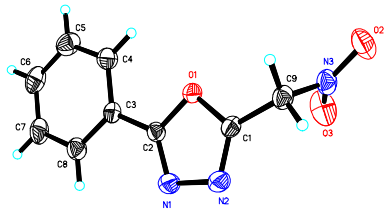
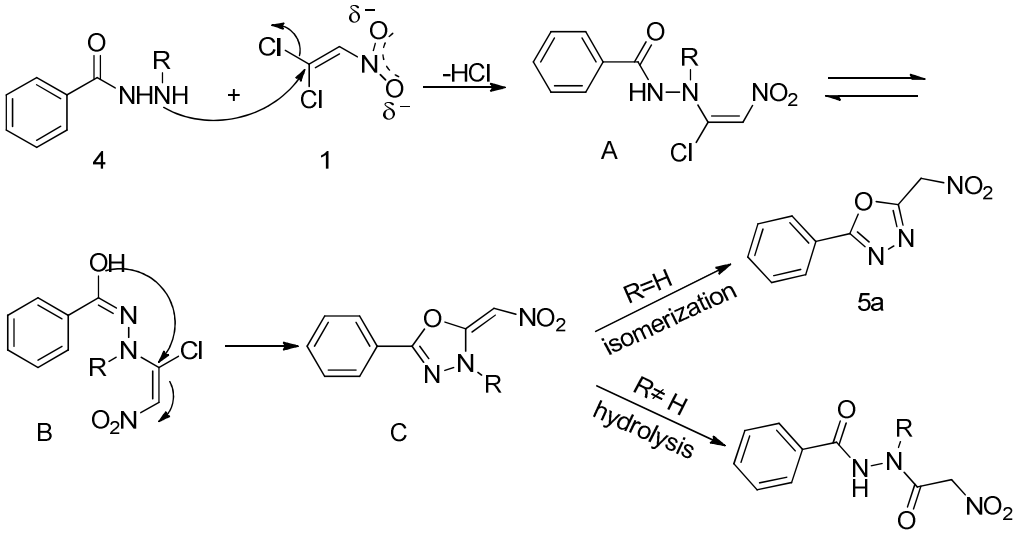


Fig. 2. crystal structure of **5a**



Scheme 2. Possible mechanism of formation of AODA from DCNE and BHA

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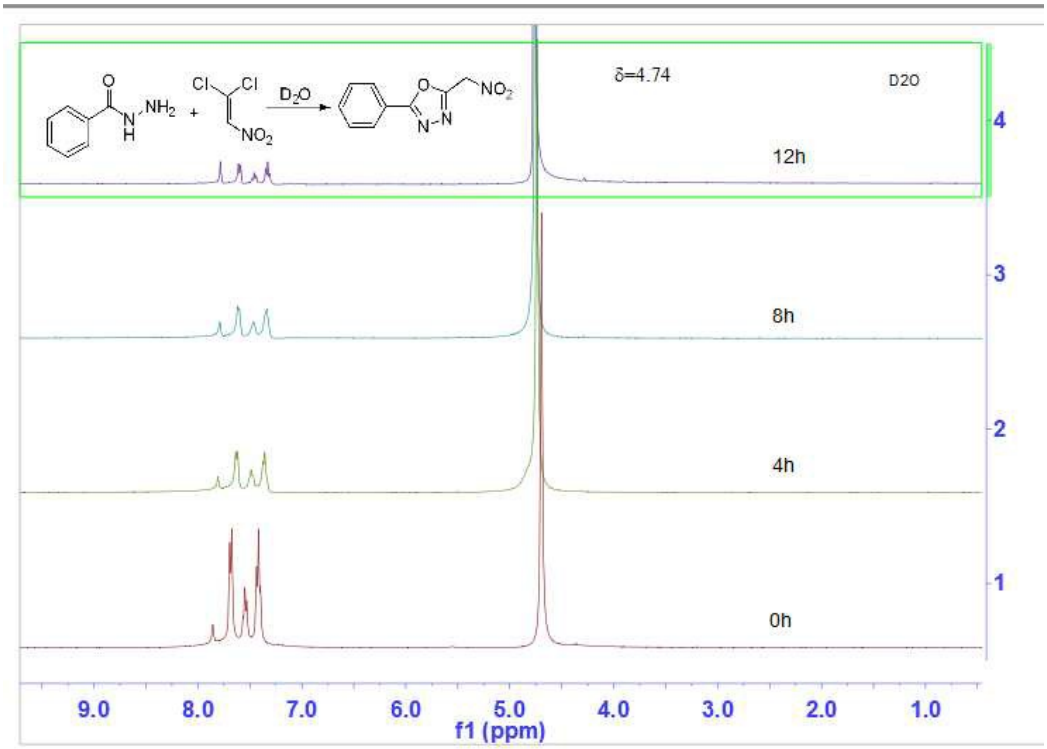

Fig. 4. ^{1}H NMR tracking of the formation of AODA

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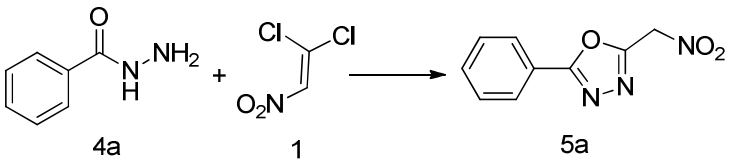
Table 1. Optimization of the formation of AODA **5a**



4a 1 5a

Entry	Temp (°C)	Solvent	Time (h)	Yield (%)
1	r.t.	chloroform	96	52[a]
2	r.t.	dichloromethane	96	50[a]
3	r.t.	ethyl acetate	96	48[a]
4	r.t.	acetonitrile	96	47[a]
5	r.t.	THF	96	43[a]
6	r.t.	1,2-dichloroethane	96	42[a]
7	r.t.	acetone	96	40[a]
8	r.t.	ethanol	96	26[a]
9	r.t.	methanol	96	20[a]
10	r.t.	toluene	96	58[a]
11	40	toluene	53	49[a]
12	60	toluene	53	54[a]
13	85	toluene	53	76[a]
14	85	toluene	24	50[a]
15	reflux	toluene	2	95[a]
16	r.t.	H_2O	12	90[b]
17	50	H_2O	3	90[b]
18	80	H_2O	3	80[b]

[a]UPLC yield. [b]Product was isolated by filtration.

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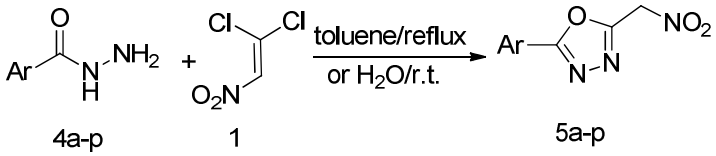
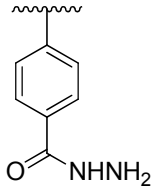
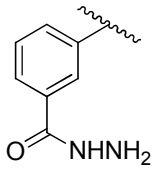
Table 2. Substrate scope investigation



Entry	Ar	5	Toluene/reflux		H_2O/r.t.	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	Ph	5a	2	94	12	90[b]
2	2-NO_2-Ph	5b	4.5	88	12	91[b]
3	3-NO_2-Ph	5c	10	85	12	93[b]
4	4-NO_2-Ph	5d	12	82	12	94[b]
5	2-CH_3-Ph	5e	2	94	12	92[a]
6	3-CH_3-Ph	5f	2	93	12	96[b]
7	4-CH_3-Ph	5g	2	93	12	91[b]
8	2-F-Ph	5h	2	91	12	90[b]
9	4-F-Ph	5i	3	92	12	90[b]
10	3-Br-Ph	5j	7	88	12	88[b]
11	2-Cl-Ph	5k	2	93	12	90[a]
12	4-*tert*-Bu-Ph	5l	2	90	12	90[b]
13	3,4,5-trimethoxy-Ph	5m	10	80	12	93[b]
14	2-Thienyl	5n	/	/	11	85[b]
15		5o	/	/	12	92[b]
16		5p	/	/	12	92[b]

[a]Product was isolated by column chromatography. [b]Product was isolated by filtration.

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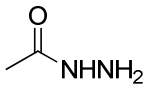
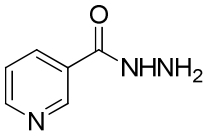
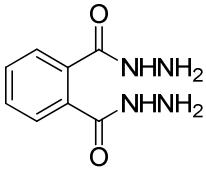
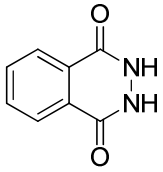
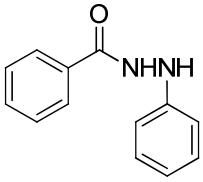
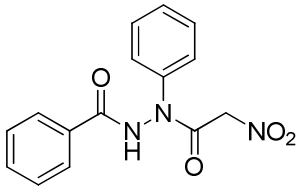
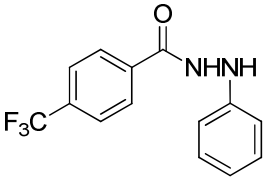
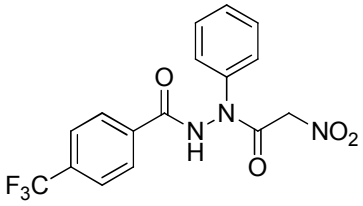
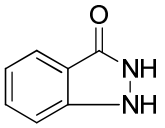
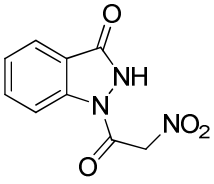
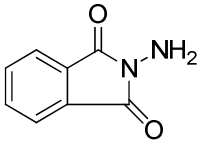
Table 3. Unsuccessful hydrazide substrates for AODA formation using water at room temperature

Entry	Hydrazide	Time (h)	Product	Yield (%)[b]
1		n.r.	n.r.	n.r.
2[c]		–	–	–
3		12		50
4		12		74
5		7[a]		57
6		12		45
7[c]		–	–	–

[a]H_2O 55°C. [b]Product was isolated by filtration. [c]unseparated products

Conclusion

In summary, we established a high efficient synthetic method for green synthesis of biologically important 2-aryl-1,3,4-oxidiazoles via application of BHA and DCNE. The water-based and catalyst-free reaction described here present several advantages over the exiting methods, which meets the requirements for green chemistry. In addition, many natural products contain hydrazide substructure, this new method may provide practicable derivertized procedure for these sensitive natural molecules.

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Experimental

Melting points (mp) were recorded on Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) spectrometer with DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High-resolution electron mass spectra (ESI-TOF) were performed on a Micromass LC-TOF spectrometer. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light. Chromatographic analysis was performed using an ACQUITY UPLC-H Class system (Waters Corp., USA), equipped with BEH C18 reversed phase column with 50 mm×2.1 mm i.d. and 1.7 μm particle size, equipped with a quaternary solvent delivery system, a 48-vial autosampler (10 μL loop), and a photodiode array detector (PDA). The UPLC separations were carried out using gradient separation at a flow rate of 0.4 mL min^{-1}. The mobile phase was a mixture of MilliQ ultrapure water (A) and acetonitrile (B). The following elution gradient totally lasted 15 min: initial mobile-phase composition, 90:10 (v/v) phase A:B; 0-3.5 min, linear change from 10 to 45% B; 3.5-7 min, linear change from 45 to 60% B; 7-8 min linear change from 60 to 100% B; 8-10 min 100% B; 10-11 min, 90:10 (v/v) phase A:B. The column and injection chamber were maintained at 40 and 25 °C, respectively. The sample injection volume was 3 μL and the detector was set at 321 nm. Gaussian09 calculated the electron cloud density and Multiwfn plotted electron cloud density map.

Procedure for the preparation of some hydrazides

Phthalohydrazide, *N′*-phenyl-4-(trifluoromethyl)benzohydrazide and *N′*-phenylbenzohydrazide were synthesized according to the reported procedures.[43,44]

General procedure for the preparation of compounds

Toluene as the solvent*:* A mixture of hydrazide (1 mmol) and DCNE (1.2 mmol) in 10 mL toluene was heated to reflux for 2-10 h. After completion of the reaction (TLC), the mixture was purified by column chromatography eluting with petroleum ether / acetic ester (3:1) and afforded the desired product.

Water as the solvent*:* A mixture of hydrazide (1 mmol) and DCNE (1.2 mmol) in 10 mL H_2O was stirred at room temperature or higher temperature for 7-12 h. After completion of the reaction (TLC), the product precipitated from the reaction mixture and was separated by filtration.

Acknowledgements

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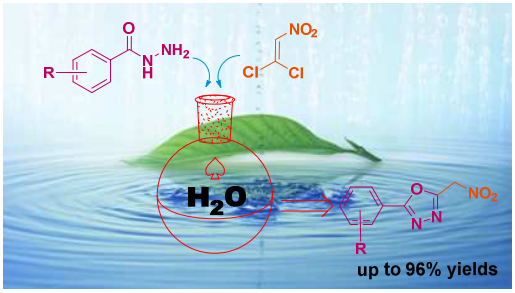

The image of Construction of 2-Aryl-1,3,4-oxadiazole Derivatives from 1,1-Dichloro-2-nitroethene and Hydrazides

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