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Novel One-Pot, Four-Component Condensation Reaction: An Efficient Approach for the Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazole Derivatives by a Ugi-4CR/*aza*-Wittig Sequence

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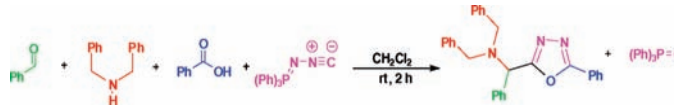
ABSTRACT



A novel and efficient method has been developed for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives using (*N*-isocyanimino)triphenylphosphorane, a secondary amine, a carboxylic acid, and an aromatic aldehyde in CH_2Cl_2 at ambient temperature in high yields without using any catalyst or activation. The procedure provides an alternative method to the synthesis of fully substituted 1,3,4-oxadiazole derivatives.

Multicomponent reactions (MCRs) are important for generating high levels of diversity, as they allow more than two building blocks to be combined in a practical, time-saving, one-pot operation, giving rise to complex structures by simultaneous formation of two or more bonds.[1] As a special subclass, the isocyanide-based MCRs (IMCRs) offer a number of advantages originating from the unique reactivity of an isocyanide, which acts as a nucleophile and an electrophile at the same time. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption, and waste production.[2] MCRs, which lead to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of "drug-like" molecules. Furthermore, the discovery of novel MCRs can be considered as an interesting topic for academic research, which also satisfies a practical interest of applied science.[3]

The *aza*-Wittig reactions of iminophosphoranes have attracted much attention in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds since they were first prepared in 1919 by Staudinger and Meyer.[4] Several interesting heterocyclization reactions involving iminophosphoranes have been reviewed. These compounds can easily be converted through an *aza*-Wittig reaction with isocyanates, carbon dioxide, or carbon disulfide into functionalized heterocumulenes which exhibit a rich

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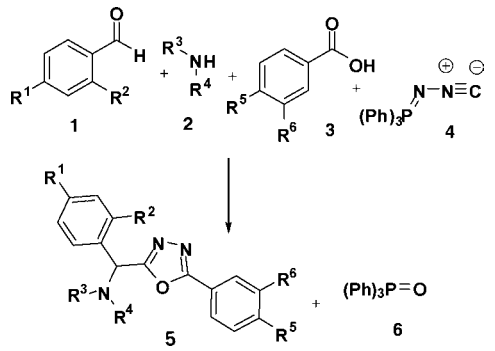
chemistry of unusual synthetic promise.[5] The nucleophilicity at the nitrogen is a factor of essential mechanistic importance in the use of these iminophosphoranes as *aza*-Wittig reagents. Iminophosphoranes are important reagents in synthetic organic chemistry, especially in the synthesis of naturally occurring products, compounds with biological and pharmacological activity.[5] There are several reports for the use of (*N*-isocyanimino)triphenylphosphorane **4** in the synthesis of metal complexes. However, the organic chemistry of **4** remains almost unexplored. The (*N*-isocyanimino)triphenylphosphorane **4** is expected to have synthetic potential because it provides a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality (Scheme 1).[6]

Scheme 1. Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazole Derivatives **5a**−**o**



Oxadiazoles have often been described as bioisoesteres for amides and esters. Due to the increased hydrolytic and metabolic stability of the oxadiazole ring, improved pharmacokinetic and in vivo performance is often observed, which make this heterocycle an important structural motif to the pharmaceutical industry.[7] As a consequence of these characteristics, 1,3,4-oxadiazoles have impacted numerous drug discovery programs, including CNS stimulant, antiinflammatory, hypotensive,[8] insecticidal,[9] hypoglycemic,[10] analgesic, anticonvulsive, antiemetic, diuretic,[11] tyrosinase inhibitor,[12] growth hormone secretagogues,[13] benzodiazepine receptor partial agonists,[14] dopamine transporters,[15] and 5-HT agonists[16] (Figure 1).

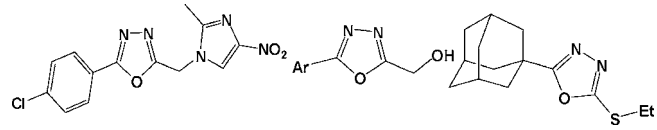


Figure 1. Examples of some biologically active 2,5-disubstituted 1,3,4-oxadiazole derivatives.

Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazole heterocycles which are multistep in nature. The most general method involves the cyclization of diacylhydrazides with a variety of reagents, such as thionyl chloride, phosphorus oxychloride, or sulfuric acid, usually under harsh reaction conditions.[17] Few reliable and operationally simple examples have been reported for the one-step synthesis of 1,3,4-oxadiazoles, especially from readily available carboxylic acids and acid hydrazides.[18] Therefore, development of a synthetic method that could be used to prepare a variety of these templates remains an important task.

As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[19] herein we wish to report a fundamentally new approach to the synthesis of 2,5-disubstituted 1,3,4-oxadia-

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Table 1. Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazole Derivatives **5a**−**o** from Benzaldehyde **1**, Secondry Amine **2**, and Carboxylic Acid **3** in the Presence of (*N*-Isocyanimino)triphenylphosphorane **4**

	aldehyde **1**	secondry amine **2**	carboxylic acid **3**	product
1	benzaldehyde	dibenzylamine	benzoic acid	**5a**
2	benzaldehyde	*N*-methylbenzyl amine	benzoic acid	**5b**
3	benzaldehyde	dibenzylamine	4-fluorobenzoic acid	**5c**
4	benzaldehyde	*N*-methylbenzyl amine	4-fluorobenzoic acid	**5d**
5	benzaldehyde	dibenzylamine	3-fluorobenzoic acid	**5e**
6	benzaldehyde	*N*-methylbenzyl amine	3-fluorobenzoic acid	**5f**
7	benzaldehyde	dibenzylamine	4-bromobenzoic acid	**5g**
8	benzaldehyde	*N*-methylbenzyl amine	4-bromobenzoic acid	**5h**
9	4-chloro benzaldehyde	dibenzylamine	4-bromobenzoic acid	**5i**
10	3-chloro benzaldehyde	dibenzylamine	4-bromobenzoic acid	**5j**
11	benzaldehyde	*N*-methylbenzyl amine	3-bromobenzoic acid	**5k**
12	benzaldehyde	dibenzylamine	4-chlorobenzoic acid	**5l**
13	4-chloro benzaldehyde	piperidine	4-iodobenzoic acid	**5m**
14	4-chloro benzaldehyde	diethylamine	4-iodobenzoic acid	**5n**
15	benzaldehyde	*N*-methylbenzyl amine	biphenyl-4-carboxylic acid	**5o**

zoles by the multicomponent reaction between (*N*-isocyanimino)triphenylphosphorane, secondary amine, benzaldehyde derivatives, and various carboxylic acids, followed by an *aza*-Wittig cyclization in CH_2Cl_2 at ambient temperature in high yields (Scheme 1).[20]

This route permits us to introduce great molecular diversity under mild reaction conditions, including substitution and scaffold diversity. A large number of derivatives can be rapidly synthesized in excellent purity and high yield by using this method.

The structures of the products were deduced from their IR, Mass, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values. The ^{1}H NMR spectrum of **5a** consisted of an AB-quartet for 2 CH_2 of benzyl groups at $\delta = 3.65$ and 3.90 ($^2J_{HH} = 13.8$ Hz), a singlet at $\delta = 5.5$ for CH, and a multiplet at $\delta = 7.21-7.72$ and 8.03−8.07 for H-aromatic. The ^{1}H-decoupled ^{13}C NMR spectrum of **5a** is in agreement with the proposed structure. In view of the success of the above-mentioned reaction, we explored the scope of this promising reaction by varying the structure of the benzaldehyde, amine, and carboxylic acid component (Table 1).

As indicated in Figure 2 and Scheme 1, the reaction proceeds very cleanly under mild reaction conditions at room temperature, and no undesirable byproducts were observed. Owing to the great diversity of substitution patterns, this reaction may be used in the production of combinatorial libraries.

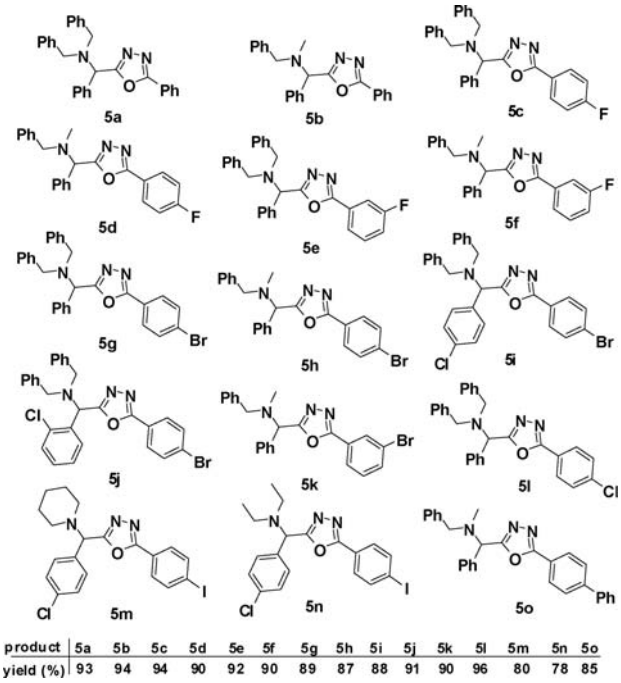


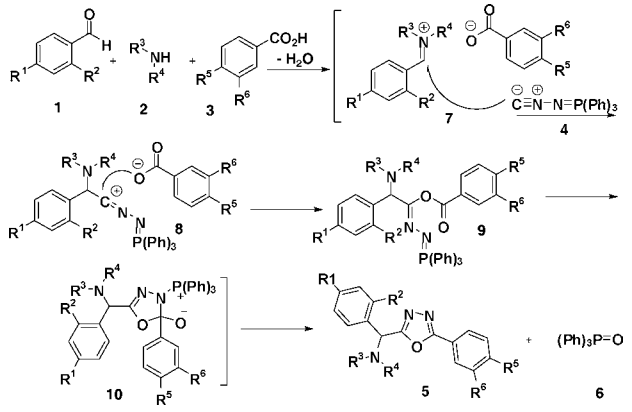
Figure 2. Synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives.

A mechanistic rationalization for this reaction is provided in Scheme 2. It is conceivable that the initial event is the condensation of the benzaldehyde **1**, secondary amine **2**, and carboxylic acid **3** entities to an intermediate iminium ion **7**. Nucleophilic addition of the (*N*-isocyanimino)triphenylphosphorane **4** to the intermediate iminium ion **7** leads

(20) **Representative experimental procedure and spectral data**: To a magnetically stirred solution of dibenzylamine (1 mmol), benzaldehyde (1 mmol), and (*N*-isocyanimino)triphenylphosphorane (1 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of benzoic acid (1 mmol) in CH_2Cl_2 (5 mL) at room temperature over 15 min. The mixture was stirred for 2 h. The solvent was removed under reduced pressure, and the viscous residue was purified by flash column chromatography (silica gel powder; petroleum ether-ethyl acetate (2:1)) to afford **5a** (93%) as a colorless oil. IR (KBr) (ν_{max}/cm^{-1}): 3471, 3028, 2925, 1551, 1492, 1451, 1070, and 747. ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 3.65 and 3.90 (AB quartet, 4 H, $2J_{HH} = 13.8$ Hz, 2 CH_2 of Benzyl groups), 5.45 (s, 1 H, CH), 7.21−7.72, and 8.03−8.07 (m, 20 H, arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C (ppm) 54.55 (2 CH_2 of Benzyl groups), 59.62 (CH), 127.00, 127.23, 128.17, 128.41, 128.59, 128.85, 129.07, and 131.79 (20 CH of arom), 123.83, 136.71, and 138.84 (4 $C_{ipso(C=C)}$ of 4 C_6H_5), 164.73 and 165.15 (2 C=N). Anal. Calcd for $C_{33}H_{33}N_3O$: C, 81.28; H, 6.82; N, 8.62. Found: C, 81.20; H, 6.77; N, 8.58.

to nitrilium intermediate **8**. This intermediate may be attacked by conjugate base of the acid **3** to form 1:1:1 adduct **9**. This adduct may undergo an intramolecular *aza*-Wittig reaction of an iminophosphorane moiety with the ester carbonyl group to afford the isolated 2,5-disubstituted 1,3,4-oxadiazole **5** by removal of triphenylphosphine oxide **6** from intermediate **10**.

Scheme 2. Possible Mechanism for the Formation of Products **5a**−**o**



In practice, the use of the (*N*-isocyanimino)triphenylphosphorane as an isocyanide input and a secondary amine allows an intramolecular *aza*-Wittig reaction after the formation of the imino−anhydride intermediate typical of the Ugi reaction. The use of a secondary amine is vital as the Mumm rearrangement is no longer possible.[21]

To the best of our knowledge, this is the first report in which (*N*-isocyanimino)triphenylphosphorane **4** was used in a four-component condensation and followed by an intramolecular *aza*-Wittig[22] ring closure of the iminophosphorane moiety with the ester carbonyl.

In conclusion, we are reporting a new MCR, yielding 2,5-disubstituted 1,3,4-oxadiazole derivatives, by a sequence of multicomponent reactions and an intramolecular *aza*-Wittig closure. Due to the easy availability of the synthetic approach and the neutral ring closure conditions, this new synthetic approach discussed here has the potential in synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles, which are of considerable interest as potential biologically active compounds or pharmaceuticals.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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