

One-pot synthesis of ferrocene-containing 1,3,4-oxadiazole derivatives from *N*-isocyaniminotriphenylphosphorane (Ph_3PNNC), cyclic ketones and ferrocene carboxylic acid

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Abstract

Reaction of *N*-isocyaniminotriphenylphosphorane with cyclic ketones in the presence of ferrocene carboxylic acid proceeded smoothly at room temperature and in neutral conditions to afford ferrocene-containing 1,3,4-oxadiazole derivatives in high yields. The reaction proceeded smoothly and cleanly under mild conditions and no side reactions were observed. The structures of the products were deduced from their IR, ¹HNMR, and ¹³CNMR spectra.

Keywords: *N*-isocyaniminotriphenylphosphorane; intramolecular *aza*-wittig reaction; 1,3,4-oxadiazole; ferrocene carboxylic acid; cyclic ketones.

Introduction

Multicomponent reaction (MCR) is a synthetic methodology in which the products can be obtained in one pot with much fewer steps [1]. In 1921 Passerini et al. have reported the three-component reaction and Ugi in 1962 reported one-pot condensation of four components [2,3]. Organophosphorus compounds have been extensively employed in organic synthesis, as well as ligands, in a number of transition metal catalysts [4]. Iminophosphoranes are important synthetic intermediates in organic chemistry especially in the preparation of naturally occurring products, compounds with biological and pharmacological activity [5-8]. During recent years, several preparative procedures have been reported for the

preparation and synthetic applications of iminophosphoranes [9-11]. The unique synthetic potential of iminophosphoranes results from the presence of electronrich nucleophilic nitrogen atoms and electrophilic phosphorus atoms as $\text{P}^+ \text{N}^-$ bonds in their structures. The structural properties of the $\text{P}^+ \text{N}^-$ bond and its chemical reactivity have been investigated through theoretical, spectroscopic and crystallographic investigations [12]. The presence of the $\text{P}^+ \text{N}^-$ bond in the iminophosphoranes' structures is a factor of essential mechanistic importance in their applications as *aza*-Wittig reagents [13]. The intramolecular *aza*-Wittig reaction has attracted attention recently because of its applications preparing

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nitrogen-containing heterocyclic compounds. Moreover, it can result from the rapid progress in the synthesis of iminophosphorane derivatives as starting materials.

There are several reports on the use of *N*-isocyaniminotriphenylphosphorane **3** in preparing metal complexes [14] (Figure 1). However, the role of *N*-isocyaniminotriphenylphosphorane **3** in organic chemistry remains almost unexplored. The *N*-isocyaniminotriphenylphosphorane **3** is expected to have unique synthetic potential because it provides a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality [15].

1,3,4-Oxadiazoles have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides [16-18]. They are an important class of heterocyclic compounds that have a wide range of pharmaceutical and biological activities including antimicrobial, antifungal, anti-inflammatory, antihypertensive, analgesic, antibacterial, hypoglycemic, antimalarial, antitubercular and antidepressant [19-23]. Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles [24,25]. These protocols are multi-step in nature [26,27]. The most generally accepted method involves the cyclization of diacylhydrazides with a variety of reagents, such as SOCl₂, POCl₃, or H₂SO₄, usually under harsh reaction conditions [28-31]. A reliable and simple method has been reported

by the Ramazani research group for the one-pot synthesis of 1,3,4-oxadiazole derivatives from carboxylic acids and *N*-isocyaniminotriphenylphosphorane **3** [32].

Ferrocene was first prepared unintentionally in 1951 [33,34]. The terms "sandwich compound" and "metallocene" are applied today, not only to ferrocene and its derivatives but also to a much wider range of compounds that include other metals [35]. The stability of ferrocene in aqueous and aerobic media, the accessibility of a large variety of derivatives and its favorable electrochemical properties as well as its biologically non-toxic effect have made ferrocenyl compounds very popular molecules for biological applications [36-44].

Many reports have investigated high activeness of some ferrocene derivatives in vitro and in vivo, against several diseases such as fungal and bacterial infections, malaria, human immunodeficiency virus (HIV) and cancer [24-29].

As part of our ongoing program to develop efficient and robust methods for the synthesis of heterocyclic compounds [14, 45, 46], we sought to develop a convenient preparation of ferrocene containing 1,3,4-oxadiazole **4** from *N*-isocyaniminotriphenylphosphorane **3**, Cyclic ketones **1** and ferrocene carboxylic acid **2** in excellent yields under neutral conditions.

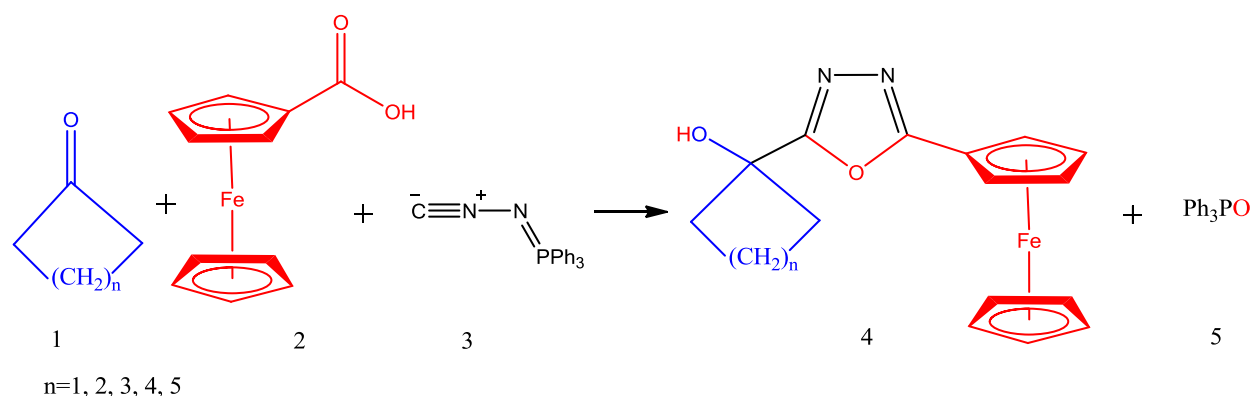


Figure 1. Synthesis of sterically congested 2,5-disubstituted 1,3,4-oxadiazoles derivatives from *N*-isocyaniminotriphenylphosphorane **3**, cyclic ketone **1** and ferrocene carboxylic acid **2**

Experimental

General

N-Isocyaniminotriphenylphosphorane (Ph₃PNNC) **3** was prepared based on reported procedures [14]. Other starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to follow the reactions were TLC and NMR. TLC and NMR indicated that there was no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ¹H and ¹³C NMR spectra were measured (CDCl₃ solution) with a BRUKER DRX-250 AVANCE spectrometer at 250.0 and 62.5 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Preparative layer chromatography (PLC) plates were prepared from Merck silica gel (F₂₅₄) powder.

Typical procedure for the preparation of compounds **4a**

To a magnetically stirred solution of *N*-isocyaniminotriphenylphosphorane **3** (1 mmol) and cyclobutanone **1** (1 mmol) in CH₃CN (7 mL) was added dropwise a solution of ferrocene carboxylic acids **2** (1 mmol) in CH₃CN

(5 mL) at room temperature over 15 min. The mixture was stirred for 20 h. The solvent was removed under reduced pressure and the viscous residue was purified by preparative layer chromatography (PLC) plates (Merck silica gel (F₂₅₄) powder); petroleum ether-ethyl acetate (3:1). The solvent was removed under reduced pressure and the products were obtained. The characterization data of the compounds are given below:

1-(5-Ferrocenyl-1,3,4-oxadiazol-2-yl)cyclobutanol (**4a**)

Dark goldenrod solid; yield: 85%; m.p. 119-121 °C; IR (KBr): 3210, 3080, 2910, 2850, 1701, 1590, 1087 and 821 cm⁻¹; ¹H NMR (250.0 MHz, CDCl₃): δH (ppm) 1.91-2.04 (m, 2H, cyclobutane), 2.49-2.56 (m, 2H, cyclobutane), 2.74-2.81 (m, 2H, cyclobutane), 5.41 (s, 1H, OH), 4.17 (s, 5H, ferrocene), 4.47 (s, 2H, ferrocene), 4.94 (s, 2H, ferrocene). ¹³C NMR (62.5 MHz, CDCl₃) δC (ppm) 12.8 and 35.43 (2CH₂, cyclobutane) 71.2 (C, cyclobutane), 66.2 (C-ferrocene), 68.1, 69.9, 70.1 (9CH- ferrocene). 166.6 and 169.3 (2C=N). Anal. Calcd for C₁₆H₁₆FeN₂O₂ (324.06): C, 59.28; H, 4.98; N, 8.64. Found: C, 58.21; H, 4.85; N, 8.91.

1-(5-Ferrocenyl-1,3,4-oxadiazol-2-yl)cyclopentanol (4b)

Dark goldenrod solid; yield: 81%; m.p. 124-126 °C; IR (KBr): 3425, 3110, 2890, 2820, 1650, 1589, 1086 and 820 cm^{-1} ; ^1H NMR (250.0 MHz, CDCl_3): δH (ppm) 1.91-2.01 and 2.25-2.35 (m, 8H, cyclopentane), 5.42 (s, 1H, OH), 4.17 (s, 5H, ferrocene), 4.47 (s, 2H, ferrocene), 4.95 (s, 2H, ferrocene). ^{13}C NMR (62.5 MHz, CDCl_3) δC (ppm) 23.84, 39.96 (4 CH_2 , cyclopentane), 77.50 (C, cyclopentane), 66.7 (C-ferrocene), 68.1, 69.9, 70.1 (9CH-ferrocene). 153.23 and 162.3 (2C=N). Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{FeN}_2\text{O}_2$ (338.07): C, 60.38; H, 5.37; N, 8.28. Found: C, 60.12; H, 5.45; N, 8.31.

1-(5-Ferrocenyl-1,3,4-oxadiazol-2-yl)cyclohexanol (4c)

Dark goldenrod solid; yield: 82%; m.p. 128-130 °C; IR (KBr): 3386, 3150, 2932, 2854, 1701, 1593, 1089 and 822 cm^{-1} ; ^1H NMR (250.0 MHz, CDCl_3): δH (ppm) 1.44-1.48, 1.58-1.61 (m, 6H, cyclohexane), 1.82-2.18 (m, 4H, cyclohexane), 5.48 (s, 1H, OH), 4.17 (s, 5H, ferrocene), 4.47 (s, 2H, ferrocene), 4.94 (s, 2H, ferrocene). ^{13}C NMR (62.5 MHz, CDCl_3) δC (ppm) 21.63, 25.05 and 36.16 (5 CH_2 , cyclohexane) 76.51 (C, cyclohexane), 68.13 (C-ferrocene), 68.1, 69.8, 70.1 (9CH-ferrocene). 167.1 and 169.5 (2C=N). Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{FeN}_2\text{O}_2$ (324.06): C, 59.28; H, 4.98; N, 8.64. Found: C, 58.21; H, 4.85; N, 8.91.

1-(5-Ferrocenyl-1,3,4-oxadiazol-2-yl)cycloheptanol (4d)

Dark goldenrod solid; yield: 80%; m.p. 109-111 °C; IR (KBr): 3410, 3151, 2933, 2855, 1694, 1593, 1089 and 820 cm^{-1} ; ^1H NMR (250.0 MHz, CDCl_3): δH (ppm) 1.46-1.56, 1.56-1.81 (m, 8H, cycloheptane), 1.50-1.52 (m, 4H, cycloheptane), 5.48 (s, 1H, OH), 4.19 (s,

5H, ferrocene), 4.36 (s, 2H, ferrocene), 4.84 (s, 2H, ferrocene). ^{13}C NMR (62.5 MHz, CDCl_3) δC (ppm) 41.8, 20.3, 30.1 (6 CH_2 , cycloheptane) 78.1 (C, cycloheptane), 68.13 (C-ferrocene), 68.1, 69.8, 70.1 (9CH-ferrocene). 160.3 and 163.4 (2C=N). Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{FeN}_2\text{O}_2$ (366.12): C, 62.31; H, 6.06; N, 7.65. Found: C, 62.28; H, 6.08; N, 7.63.

1-(5-Ferrocenyl-1,3,4-oxadiazol-2-yl)cyclooctanol (4e)

Dark goldenrod solid; yield: 83%; m.p. 118-120 °C; IR (KBr): 3410, 3090, 2900, 2820, 1701, 1600, 1091 and 821 cm^{-1} ; ^1H NMR (250.0 MHz, CDCl_3): δH (ppm) 1.10-1.32 (m, 8H, cyclooctane), 1.69-1.81 (m, 4H, cyclooctane), 5.52 (s, 1H, OH), 4.20 (s, 5H, ferrocene), 4.34 (s, 2H, ferrocene), 4.88 (s, 2H, ferrocene). ^{13}C NMR (62.5 MHz, CDCl_3) δC (ppm) 18.2, 29.69, 41.3 (10 CH_2 , cyclooctane), 77.64 (C, cyclooctane), 69.83-71.11, 76.54-77.56 (m, 9CH-ferrocene). 167.1 and 169.5 (2C=N). Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{FeN}_2\text{O}_2$ (380.12): C, 63.17; H, 6.36; N, 7.37. Found: C, 63.28; H, 6.42; N, 7.41.

Results and discussion

As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds [46-51], we sought to develop a convenient preparation of 1,3,4-oxadiazoles **4** from ferrocene carboxylic acids **2** and *N*-isocyaniminotriphenylphosphorane **3** in excellent yields under neutral conditions (Figure 1).

Ferrocene carboxylic acid **2** with cyclic ketones **1** and *N*-isocyaniminotriphenylphosphorane **3** in CH_3CN react together in a 1:1:1 ratio at room temperature to produce sterically congested 2,5-disubstituted 1,3,4-

oxadiazoles **4** and triphenylphosphine oxide **5** (Figure 1 and Table 1).

The reaction proceeds smoothly and cleanly under mild conditions. The suggested mechanism for this reaction is provided in Figure 2. On the basis of the chemistry of isocyanides, it is reasonable to assume that the first step may involve nucleophilic addition of the *N*-isocyaniminotriphenylphosphorane **3** to cyclic ketones **1** which is facilitated by its protonation with acid **2** leading to nitrilium intermediate **6**. This intermediate may be attacked by conjugate base of the acid **2** in order to form 1:1:1 adduct **7**. This adduct may undergo an intramolecular *aza*-Wittig reaction of iminophosphorane moiety with the ester carbonyl to afford the isolated sterically congested 1,3,4-oxadiazole derivatives **4** by the removal of triphenylphosphine oxide **5** from intermediate **8** (Figure 2).

The structures of the products **4a** were deduced from their IR, ^1H , and ^{13}C NMR spectra. The ^1H NMR spectrum of **4a** exhibited 3 multiplets

for the cyclobutane ($\delta = 1.91\text{--}2.04$, $2.49\text{--}2.56$ and $2.74\text{--}2.81$ ppm), a singlet for OH ($\delta = 4.28$), a sharp singlet at $\delta = 4.16$ ppm for C_5H_5 ring, two singlet at $\delta = 4.47$ ppm and 4.94 ppm for C_5H_4 . The ^1H -decoupled ^{13}C NMR spectrum of **4a** is in agreement with the proposed structure that are in agreement with the formula structure of **4a**. Partial assignment of these resonances is given in the spectral analysis section (see Experimental section).

In summary, we have found a new method for the preparation of sterically congested 2,5-disubstituted 1,3,4-oxadiazole derivatives **4** from Ferrocene carboxylic acid **2**, cyclic ketone **1** and *N*-isocyaniminotriphenylphosphorane **3** in excellent yields under neutral conditions. We think that the reported method offers a mild and simple route for the preparation of these derivatives. Its ease of work-up and reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

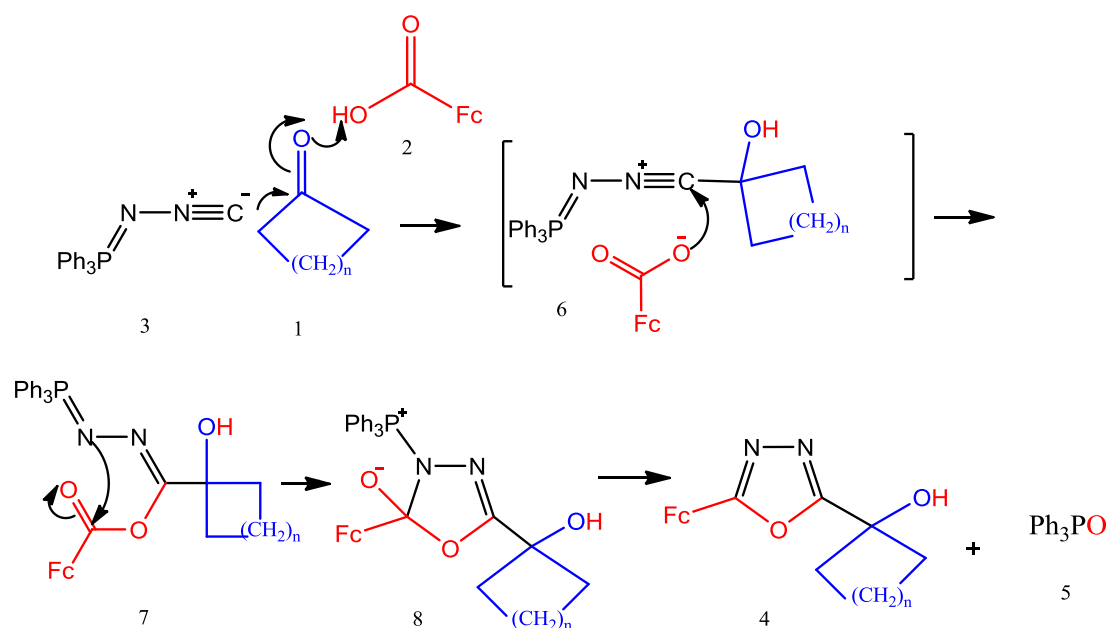
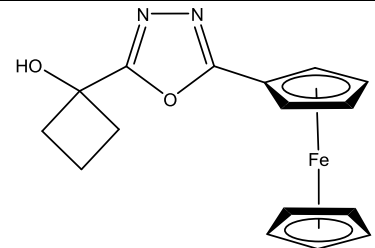
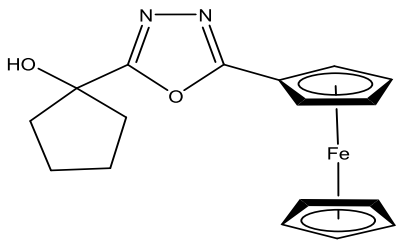
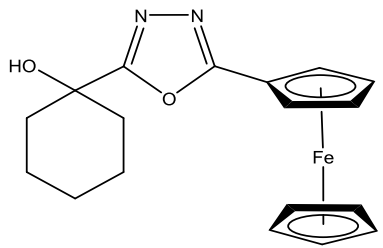
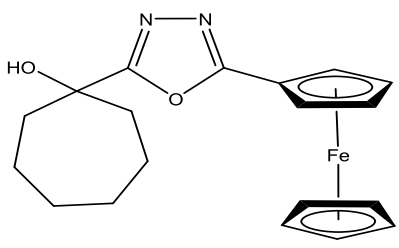
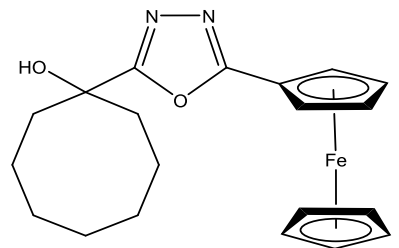


Figure 2. Proposed mechanism for the formation of disubstituted 1,3,4-oxadiazole derivatives **4**

Table1. Synthesis of 1,3,4-oxadiazole derivatives

Product	n	Yield(%)	M.p. °C	
4a	1	85	119-121	
4b	2	81	124-127	
4c	3	82	128-131	
4d	4	80	109-112	
4e	5	83	118-122	

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Conclusion

In summary, the reported method offers a mild, simple, and efficient route for

the preparation of sterically congested ferrocene-containing 1,3,4-oxadiazole derivatives **4** from cyclic ketones **1**, *N*-isocyaniminotriphenylphosphorane (Ph_3PNNC) **3**, and ferrocene carboxylic acid **2**. Its ease of workup, high yields and fairly mild reaction conditions make

it a useful addition to modern synthetic methodologies.

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