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# A facile route for the preparation of disubstituted 1,3,4-oxadiazoles from furfural, carboxylic acids, and secondary amines in the presence of *N*-isocyaniminotriphenylphosphorane

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A simple method has been developed for four-component synthesis of disubstituted 1,3,4-oxadiazoles using *N*-isocyaniminotriphenylphosphorane, a secondary amine, carboxylic acid, and furfural in $CH_2Cl_2$ by a Ugi-4CR/*aza*-Wittig sequence at room temperature in fairly high yields without using any catalyst or activation. The procedure provides an alternative method to the preparation of fully substituted 1,3,4-oxadiazoles.

**Key words:** *N*-isocyaniminotriphenylphosphorane, furfural, carboxylic acid, 1,3,4-oxadiazole, *aza*-Wittig reaction, secondary amine

## INTRODUCTION

Furan derivatives, obtained from both synthetic and natural sources, have attracted much interest due to their wide ranging pharmaceutical applications [1–3]. Many naturally occurring furans show interesting biological activities, such as cytotoxic and antitumor properties [3, 4], as well as antispasmodic [5], antimicrobial [6, 7], and several other potentially useful activities [8].

Multicomponent reactions (MCRs) have recently emerged as fairly valuable tools for generating high levels of diversity, as they allow more than two building blocks to be combined in a practical, one-pot operation, time-saving, giving rise to complex structures by simultaneous formation of two or more bonds. Isocyanide-based MCRs such as the versatile Ugi and Passerini reactions [9–14] are of special importance in this area. Isocyanide-based MCRs (IMCRs) offer a number of advantages originating from the unique reactivity of isocyanide, which acts as an electrophile and a nucleophile at the same time. MCRs, by reducing the number of energy consumption, synthetic steps, and waste production, contribute to the requirements of an environment-friendly process. MCR, which lead to interesting heterocyclic scaffolds, are particularly useful for the preparation of diverse chemical libraries of "drug-like" molecules [15, 16].

1,3,4-Oxadiazole derivatives are important classes of molecules and heterocyclic scaffolds in biologically active compounds. Oxadiazole derivatives have often been described as bioisoesters for amides and esters. They have impacted numerous drug discovery programs, including CNS stimulant, analgesic, antiinflammatory, hypoglycemic, insecticidal, antiemetic, diuretic, tyrosinase inhibitor, anticonvulsive, benzodiazepine receptor partial agonists, growth hormone secretagogues, dopamine transporters, and 5-HT agonists [17–26]. 1,3,4-Oxadiazole derivatives have attracted much attention due to their increased hydrolytic and metabolic stability of the oxadiazole ring [27–31].

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Several routes have been reported in the literature for the synthesis of oxadiazoles [32]. Among these methods, the most commonly used way is the cyclization of diacylhydrazines, with a variety of dehydration reagents, for example, thionyl chloride, phosphorous oxychloride and sulfuric acid, usually under harsh reaction conditions [33, 34]. Furthermore, the discovery of facile routes to synthesis of 1,3,4-oxadiazole derivatives can be considered as an interesting topic for academic research, which also satisfies a practical interest of applied science [35, 36].

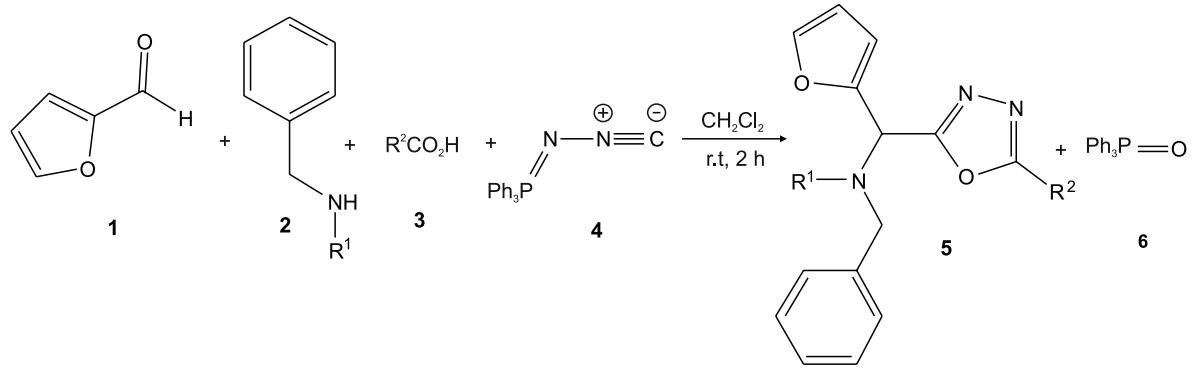
## RESULTS AND DISCUSSION

As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds via isocyanide-based multicomponent reactions [37–47], herein we wish to report a fundamentally new approach to the preparation of disubstituted 1,3,4-oxadiazoles by the multicomponent reaction between *N*-isocyaniminotriphenylphosphorane, a secondary amine, furfural, and various carboxylic acids, followed by an *aza*-Wittig cyclization in $CH_2Cl_2$ at ambient temperature in high yields (Scheme 1). This route permits us to introduce the great molecular diversity under mild reaction conditions, including substitution and scaffold diversity. A large number of 1,3,4-oxadiazoles can be rapidly synthesized in excellent purity and high yield by using this method.

The structures of the products were deduced from their $^1$H NMR, $^{13}$C NMR, mass and IR 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 a singlet at δ = 2.3 ppm for $NCH_3$, an AB-quartet for $CH_2$ of the benzyl group at δ = 3.67 ppm and 3.74 ppm ($^2J_{HH}$ = 13.2 Hz), a singlet at δ = 5.4 ppm for CH, and a multiplet at δ = 6.42–6.53 ppm and 7.30–8.03 ppm for aromatic protons of phenyl and furan. 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 amine and carboxylic acid component.

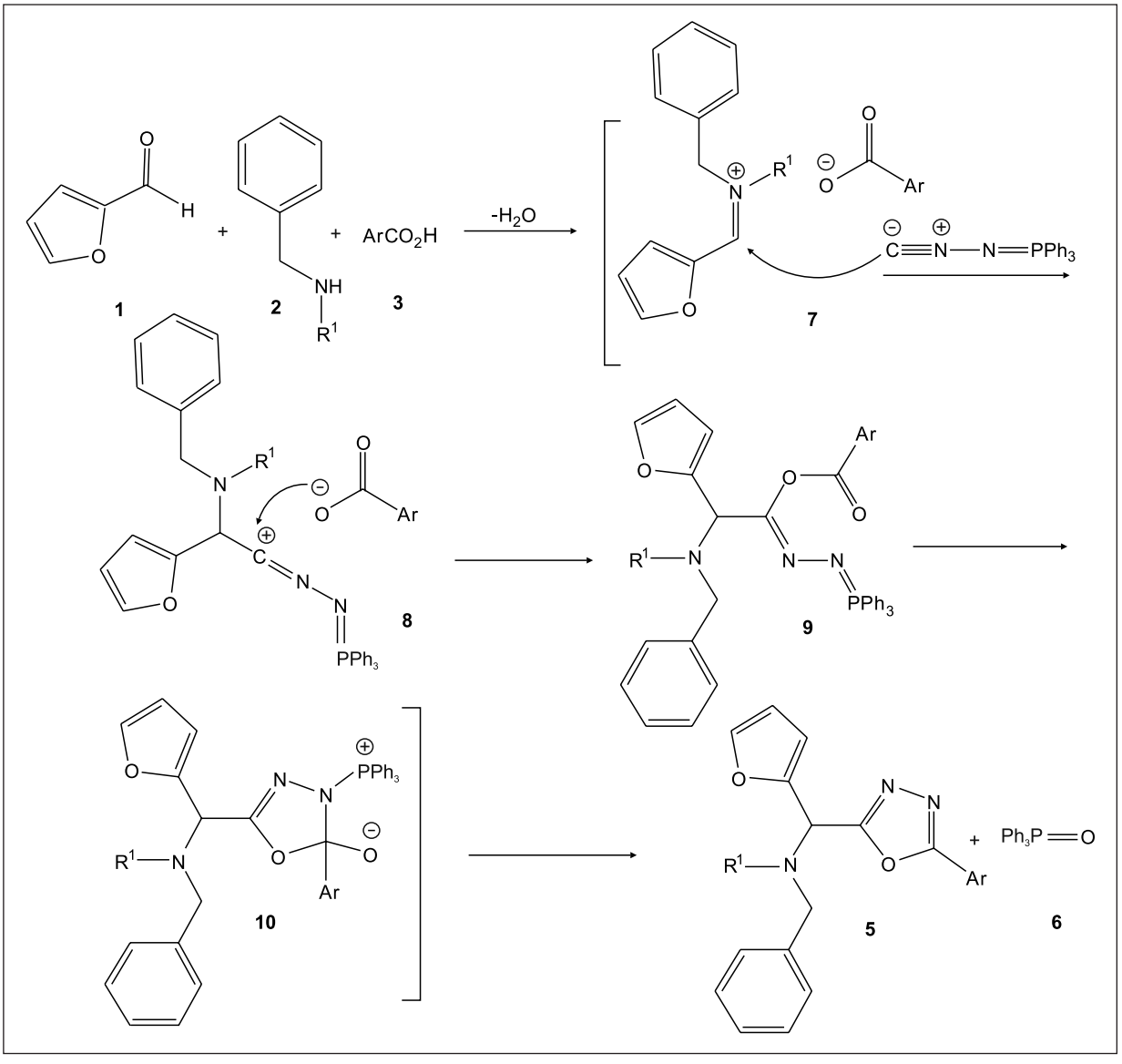
As indicated in Scheme 1, the reaction proceeds very cleanly under mild reaction conditions at room temperature, and no undesirable by-products were observed. Owing to the great diversity of substitution patterns, this reaction may be used in the production of combinatorial libraries.

A mechanistic rationalization for this reaction is provided in Scheme 2. It is conceivable that the initial event is the condensation of the furfural **1**, secondary amine **2**, and carboxylic acid **3** entities to intermediate iminium ion **7**. Nucleophilic addition of *N*-isocyaniminotriphenylphosphorane **4** to intermediate iminium ion **7** leads to nitrilium intermediate **8**. This intermediate may be attacked by the conjugate base of 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 isolated disubstituted 1,3,4-oxadiazole **5** by removal of triphenylphosphine oxide **6** from intermediate **10**. In practice, the use of *N*-isocyaniminotriphenylphosphorane 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 [48, 49].




**4a**: $R^1$ = methyl, $R^2$ = 4-chlorophenyl; **4b**: $R^1$ = benzyl, $R^2$ = 4-flourophenyl;
**4c**: $R^1$ = methyl, $R^2$ = 4-iodophenyl; **4d**: $R^1$ = methyl, $R^2$ = 4-bromophenyl;
**4e**: $R^1$ = benzyl, $R^2$ = 4-bromophenyl; **4f**: $R^1$ = benzyl, $R^2$ = 4-chlorophenyl;
**4g**: $R^1$ = methyl, $R^2$ = 3-chlorophenyl; **4h**: $R^1$ = benzyl, $R^2$ = 3-chlorophenyl;
**4i**: $R^1$ = methyl, $R^2$ = 4-flourophenyl; **4j**: $R^1$ = methyl, $R^2$ = 4-tert-butylphenyl;
**4k**: $R^1$ = methyl, $R^2$ = 4-methylphenyl-1-ethenyl; **4l**: $R^1$ = benzyl, $R^2$ = 4-methylphenyl-1-ethenyl;
**4m**: $R^1$ = methyl, $R^2$ = 4-flourophenyl-1-ethenyl; **4n**: $R^1$ = methyl, $R^2$ = 4-chlorophenyl-1-ethenyl;
**4o**: $R^1$ = benzyl, $R^2$ = phenylethynyl; **4p**: $R^1$ = methyl, $R^2$ = phenylethynyl;
**4q**: $R^1$ = ethyl, $R^2$ = phenylethynyl

**Scheme 1.** Four-component synthesis of 1,3,4-oxadiazole derivatives 5a–q




**Scheme 2.** Proposed mechanism for the formation of 1,3,4-oxadiazoles 5a–q

## EXPERIMENTAL

Starting materials and solvents were obtained from Fluka (Switzerland) and Merck (Germany) and were used without further purification. The methods used to follow the reactions were NMR and TLC. 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. $^{1}H$ and $^{13}C$ NMR spectra were measured ($CDCl_3$ 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. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. Flash chromatography columns were prepared from Merck silica gel powder.

**General procedure for the preparation of (5a–5q)**

To a stirred solution of *N*-isocyaniminotriphenylphosphorane **4** (1.0 mmol), furfural **1** (1.0 mmol) and secondry amine **2** (1.0 mmol) in $CH_2Cl_2$ (5 mL) a solution of carboxylic acids **3** (1.0 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise 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 preparative layer chromatography (silica gel 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:

***N*-benzyl[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]2-furyl-*N*-methylmethanamine (5a)**

Yellow oil, yield (96%); IR: 3 029, 2 851, 1 607, 1 484, 1 454, 1 124, 1 013, 735 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$) δ: 2.35 (s, 3H, $NCH_3$),

3.67 and 3.74 (AB quartet, 2H, $^2J_{HH}$ = 13.26 Hz, $CH_2$ of benzyl), 5.40 (s, 1H, CH), 6.42–6.53 (m, 2H, furan), 7.30–8.03 (m, 10H, CH of arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 38.88 ($NCH_3$), 57.50 ($CH_2$ of benzyl), 58.49 (CH), 110.44, 110.53 and 143.05 (3 CH of furan), 122.26 ($C_{ipso(C=C)}$ of $C_6H_4Cl$), 127.35, 128.30, 128.41, 128.90 and 129.46 (9 CH of arom), 138.13 ($C_{Ar}$-Cl of $C_6H_4Cl$), 138.17 ($C_{ipso(C=C)}$ of $C_6H_5$), 148.69 ($C_{ipso(C=C)}$ of furan), 163.67 and 164.35 (2 C=N). MS: m/e (%) 380 ($M^+$, 95), 260 (50), 269 (6), 217 (21), 200 (92), 139 (30), 120 (43), 91 (55), 65 (15), 42 (20). Anal. calcd. for $C_{21}H_{18}ClN_3O_2$ (379.8): C, 66.40; H, 4.78; N, 11.06. Found: C, 66.36; H, 4.75; N, 11.10.

**N,N-dibenzyl[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]2-furylmethanamine (5b)**

Colorless oil, yield (94%); IR: 3 029, 2 848, 1 612, 1 498, 1 454, 1 074, 1 012, 741 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 3.73 and 3.83 (AB quartet, 4 H, $^2J_{HH}$ = 13.76 Hz, 2 $CH_2$ of benzyl groups), 5.46 (s, 1H, CH), 6.42–6.53 (m, 2H, furan), 7.19–8.1 (m, 15H, CH of arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 53.83 (2 $CH_2$ of benzyl groups), 54.75 (CH), 110.39, 110.43 and 143.05 (3 CH of furan), 116.45 (d, $^2J_{CF}$ = 22.64 Hz), 120.11 (d, $^4J_{CF}$ = 3.14 Hz), 129.28 (d, $^3J_{CF}$ = 8.8 Hz), 162.42 (d, $^1J_{CF}$ = 231.43), 127.29, 128.43 and 128.75 (10 CH of arom), 138.73 (2 $C_{ipso(C=C)}$ of 2 $C_6H_5$), 149.03 ($C_{ipso(C=C)}$ of furan), 163.65 and 166.84 (2 C=N). MS: m/e (%) 440 ($M^+$, 35), 407 (5), 279 (6), 243 (99), 197 (60), 159 (30), 149 (33), 123 (80), 95 (40), 65 (35). Anal. calcd. for $C_{27}H_{22}FN_3O_2$ (439.5): C, 73.79; H, 5.05; N, 9.56. Found: C, 73.75; H, 5.09; N, 9.59.

***N*-benzyl(2-furyl)[5-(4-iodophenyl)-1,3,4-oxadiazol-2-yl]-N-methylmethanamine (5c)**

Yellow oil, yield (94%); IR: 3 028, 2 851, 1 600, 1 495, 1 454, 1 083, 1 003, 735 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.35 (s, 3H, $NCH_3$), 3.67 and 3.74 (AB quartet, 2H, $^2J_{HH}$ = 13.50 Hz, $CH_2$ of benzyl), 5.40 (s, 1H, CH), 6.41–6.52 (m, 2H, furan), 7.30–7.89 (m, 10H, CH of arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 38.89 ($NCH_3$), 57.50 ($CH_2$ of benzyl), 58.50 (CH), 98.75 ($C_{Ar}$-I of $C_6H_4I$), 110.45, 110.55 and 143.06 (3 CH of furan), 123.21 ($C_{ipso(C=C)}$ of $C_6H_4I$), 127.36, 128.35, 128.42, 128.90 and 138.36 (9 CH of arom), 138.16 ($C_{ipso(C=C)}$ of $C_6H_5$), 148.66 ($C_{ipso(C=C)}$ of furan), 163.71 and 164.59 (2 C=N). MS: m/e (%) 470 ($M^+$, 20), 352 (70), 271 (20), 231 (40), 200 (30), 174 (25), 120 (40), 91 (95), 65 (25), 42 (15). Anal. calcd. for $C_{21}H_{18}IN_3O_2$ (471.3): C, 53.52; H, 3.85; N, 8.92. Found: C, 53.55; H, 3.90; N, 8.93.

***N*-benzyl[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]2-furyl-N-methylmethanamine (5d)**

Colorless oil, yield (89%); IR: 3 028, 2 852, 1 603, 1 481, 1 454, 1 084, 1 002, 735 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.36 (s, 3H, $NCH_3$), 3.75 (m, 2H, $CH_2$ of benzyl), 5.41 (s, 1H, CH), 6.42–6.54 (m, 2H, furan), 7.30–7.96 (m, 10H, CH of arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 38.86 ($NCH_3$), 57.45 ($CH_2$ of benzyl), 58.48 (CH), 110.47, 110.52 and 143.11(3 CH of furan), 122.66 ($C_{Ar}$-Br of $C_6H_4Br$), 126.58 ($C_{ipso(C=C)}$ of $C_6H_4Br$), 127.41, 128.43, 128.95 and 132.43(9 CH of arom), 139.21 ($C_{ipso(C=C)}$ of $C_6H_5$), 149.12 ($C_{ipso(C=C)}$ of furan), 163.58 and 164.46 (2 C=N). Anal. calcd. for $C_{21}H_{18}BrN_3O_2$ (424.3): C, 59.45; H, 4.28; N, 9.90. Found: C, 59.46; H, 4.30; N, 10.0.

***N,N*-dibenzyl[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]-2-furylmethanamine (5e)**

Colorless oil, yield (93%); IR: 3 028, 2 845, 1 604, 1 481, 1 454, 1 084, 1 012, 735 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 3.73 and 3.82 (AB quartet, 4H, $^2J_{HH}$ = 13.76 Hz, 2 $CH_2$ of benzyl groups), 5.46 (s, 1H, CH), 6.42–6.51 (m, 2H, furan), 7.27–7.94 (m, 15H, CH of arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 53.88 (2 $CH_2$ of benzyl groups), 54.79 (CH), 110.40, 110.47 and 143.07 (3 CH of furan), 122.73 ($C_{Ar}$-Br of $C_6H_4Br$), 126.52 ($C_{ipso(C=C)}$ of $C_6H_4Br$), 127.30, 128.43, 128.75, and 132.44 (14 CH of arom), 138.69 (2 $C_{ipso(C=C)}$ of 2 $C_6H_5$), 148.96 ($C_{ipso(C=C)}$ of furan), 163.86 and 164.35 (2 C=N). Anal. calcd. for $C_{27}H_{22}BrN_3O_2$ (500.4): C, 64.81; H, 4.43; N, 8.40. Found: C, 64.85; H, 4.47; N, 8.39.

***N,N*-dibenzyl[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]2-furylmethanamine (5f)**

Yellow oil, yield (91%); IR: 3 029, 2 848, 1 607, 1 484, 1 454, 1 084, 1 012, 735 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 3.74 and 3.83 (AB quartet, 4H, $^2J_{HH}$ = 14.00 Hz, 2 $CH_2$ of benzyl groups), 5.46 (s, 1H, CH), 6.42–6.52 (m, 2H, furan), 7.25–8.01 (m, 15H, CH of arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 53.87 (2 $CH_2$ of benzyl groups), 54.79 (CH), 110.40, 110.47 and 143.07 (3 CH of furan), 122.30 ($C_{ipso(C=C)}$ of $C_6H_4Cl$), 127.30, 128.25, 128.43, 128.76 and 129.49 (14 CH of arom), 138.11 ($C_{Ar}$-Cl of $C_6H_4Cl$), 138.71 (2 $C_{ipso(C=C)}$ of 2 $C_6H_5$), 148.98 ($C_{ipso(C=C)}$ of furan), 163.83 and 164.27 (2 C=N). Anal. calcd. for $C_{27}H_{22}ClN_3O_2$ (455.9): C, 71.13; H, 4.86; N, 9.22. Found: C, 71.15; H, 4.87; N, 9.25.

***N*-benzyl[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl]2-furyl-N-methylmethanamine (5g)**

Yellow oil, yield (89%); IR: 3 028, 2 852, 1 617, 1 503, 1 454, 1 072, 1 016, 735 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.36 (s, 3H, $NCH_3$), 3.67 and 3.75 (AB quartet, 2H, $^2J_{HH}$ = 13.26 Hz, $CH_2$ of benzyl), 5.41 (s, 1H, CH), 6.42–6.53 (m, 2H, furan), 7.29–8.06 (m, 10H, CH of arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 38.90 ($NCH_3$), 57.51 ($CH_2$ of benzyl), 58.51 (CH), 110.46, 110.56 and 143.08 (3 CH of furan), 125.40 ($C_{ipso(C=C)}$ of $C_6H_4Cl$), 125.13, 126.98, 127.36, 128.43, 128.90, 130.45 and 131.88 (9 CH of arom), 135.21 ($C_{Ar}$-Cl of $C_6H_4Cl$), 138.15 ($C_{ipso(C=C)}$ of $C_6H_5$), 148.62 ($C_{ipso(C=C)}$ of furan), 163.85 and 164.02 (2 C=N). Anal. calcd. for $C_{21}H_{18}ClN_3O_2$ (379.84): C, 66.40; H, 4.78; N, 11.06. Found: C, 66.41; H, 4.77; N, 11.09.

***N,N*-dibenzyl[5-(3-chlolorophenyl)-1,3,4-oxadiazol-2-yl]2-furylmethanamine (5h)**

Yellow oil, yield (92%); IR: 3 028, 2 847, 1 602, 1 547, 1 454, 1 013, 740 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 3.74 and 3.83 (AB quartet, 4H, $^2J_{HH}$ = 13.76 Hz, 2 $CH_2$ of benzyl groups), 5.47 (s, 1H, CH), 6.43–6.53 (m, 2H, furan), 7.23–8.04 (m, 15H, CH of

arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 53.88 (2 $CH_2$ of benzyl groups), 54.79 (CH), 110.42, 110.50 and 143.11 (3 CH of furan), 125.43 ($C_{ipso(C=C)}$ of $C_6H_4Cl$), 125.09, 126.97, 127.33, 128.45, 128.76 , 130.48 and 131.87 (14 CH of arom), 135.21 ($C_{Ar}$-Cl of $C_6H_4Cl$), 138.68 (2 $C_{ipso(C=C)}$ of 2 $C_6H_5$), 148.90 ($_{Cipso(C=C)}$ of furan), 163.94 and 164.01 (2 C=N). Anal. calcd. for $C_{27}H_{22}ClN_3O_2$ (455.94): C, 71.13; H, 4.86; N, 9.22. Found: C, 71.15; H, 4.90; N, 9.25.

***N*-benzyl[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]2-furyl-*N*-methylmethanamine (5i)**

Colorless oil, yield (93%); IR: 3 029, 2 851, 1 612, 1 502, 1 454, 1 158, 1 013, 739 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.35 (s, 3H, $NCH_3$), 3.67 and 3.74 (AB quartet, 2H, $^2J_{HH}$ = 13.26 Hz, $CH_2$ of benzyl), 5.40 (s, 1H, CH), 6.41–6.52 (m, 2H, furan), 7.18–8.11 (m, 10H, CH of arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 38.87 ($NCH_3$), 57.49 ($CH_2$ of benzyl), 58.47 (CH), 110.43, 110.51 and 143.04 (3 CH of furan), 116.43 (d, $^2J_{CF}$ = 22.64 Hz), 120.11 (d, $^4J_{CF}$ = 3.14 Hz), 129.32 (d, $^3J_{CF}$ = 9.43 Hz), 164.49 (d, $^1J_{CF}$ = 211.31 Hz), 127.34, 128.41 and 128.90 (5 CH of arom), 138.19 ($C_{ipso(C=C)}$ of $C_6H_5$), 148.74 ($C_{ipso(C=C)}$ of furan), 163.50 and 164.35 (2 C=N). Anal. calcd. for $C_{27}H_{22}ClN_3O_2$ (363.38): C, 69.41; H, 4.99; N, 11.56. Found: C, 69.45; H, 4.95; N, 11.51.

***N*-benzyl{5-[4-(tert-butyl)phenyl]-1,3,4-oxadiazol-2-yl}2-furyl-*N*-methylmethanamine (5j)**

Yellow oil, yield (94%); IR: 3 030, 2 963, 1 616, 1 496, 1 454, 1 113, 1 014, 738 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 1.37 (s, 9H, $(CH_3)_3$), 2.35 (s, 3H, $NCH_3$), 3.66 and 3.76 (AB quartet, 2 H, $^2J_{HH}$ = 13.5 Hz, $CH_2$ of benzyl), 5.42 (s, 1H, CH), 6.40–6.54 (m, 2H, furan), 7.29–8.04 (m, 10H, CH of arom and furan); $^{13}$C NMR ($CDCl_3$) δ: 31.11(3 $CH_3$), 35.10 (C, aliphatic), 38.81 ($NCH_3$), 57.53 ($CH_2$ of benzyl), 58.41 (CH), 110.41, 110.43 and 142.97 (3 CH of furan), 120.96 ($C_{ipso(C=C)}$ of C6H4C$(CH_3)_3$), 126.07, 126.87, 127.30, 128.40 and 128.93 (9 CH of arom), 138.30 ($C_{ipso(C=C)}$ of C6H5), 148.96 ($C_{ipso(C=C)}$ of furan), 155.49 ($C_{Ar}$-C$(CH_3)_3$ of $C_6H_4C(CH_3)_3$), 163.13 and 165.22 (2 C=N). Anal. calcd. for $C_{25}H_{27}N_3O_2$ (401.25): C, 74.79; H, 6.78; N, 10.47. Found: C, 74.80; H, 6.77; N, 10.45.

***N*-benzyl(2-furyl)-*N*-methyl{5-[(*E*)-2-(4-methylphenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}methanamine (5k)**

Yellow oil, yield (87%); IR: 3 027, 2 851, 1 642, 1 609, 1 532, 1 453, 1 014, 739 cm$^{-1}$; $^1$HvNMR ($CDCl_3$) δ: 2.34 (s, 3H, $CH_3$), 2.39 (s, 3H, $NCH_3$), 3.66 and 3.73 (AB quartet, 2H, $^2J_{HH}$ = 13.50 Hz, $CH_2$ of benzyl), 5.36 (s, 1H, CH), 6.42–6.52 (m, 2H, furan), 6.99–7.57 (m, 12H, CH of arom, vinylic group and furan); $^{13}$C NMR ($CDCl_3$) δ: 21.47 ($CH_3$), 38.89 ($NCH_3$), 57.57 ($CH_2$ of benzyl), 58.44 (CH), 110.41, 110.50 and 143.01 (3 CH of furan), 108.80 and 138.21 (2 CH of vinylic), 127.32, 127.51, 128.40, 128.94 and 129.75 (9 CH of arom), 131.93, 139.42 and 140.45 (3 C of arom), 148.82 ($C_{ipso(C=C)}$ of furan), 162.79 and 164.96 (2 C=N). Anal. calcd. for $C_{24}H_{23}N_3O_2$ (385.46): C, 74.78; H, 6.01; N, 10.90. Found: C, 74.80; H, 6.00; N, 10.95.

***N,N*-dibenzyl(2-furyl){5-[(*E*)-2-(4-methylphenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}methanamine (5l)**

Yellow oil, yield (91%); IR: 3 027, 2 850, 1 642, 1 608, 1 532, 1 454, 1 013, 740 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.41 (s, 3H, $CH_3$), 3.72 and 3.83 (AB quartet, 4H, $^2J_{HH}$ = 13.76 Hz, 2 $CH_2$ of benzyl groups), 5.43 (s, 1H, CH), 6.42–6.50 (m, 2H, furan), 7.00–7.54 (m, 17H, CH of arom, vinylic group and furan); $^{13}$C NMR ($CDCl_3$) δ: 21.49 ($CH_3$), 53.81 (2 $CH_2$ of benzyl groups), 54.71 (CH), 110.38, 110.41 and 143.03 (3 CH of furan), 108.87 and 138.81 (2 CH of vinylic), 127.27, 127.52, 128.42, 128.77 and 129.76 (14 CH of arom), 131.95, 139.33 and 140.46 (4 C of arom), 149.15 ($C_{ipso(C=C)}$ of furan), 162.91 and 164.87 (2 C=N). Anal. calcd. for $C_{30}H_{27}N_3O_2$ (461.55): C, 78.01; H, 5.90; N, 9.10. Found: C, 78.04; H, 5.85; N, 9.11.

***N*-benzyl{5-[(*E*)-2-(4-fluorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}2-furyl-*N*-methylmethanamine (5m)**

Colorless oil, yield (87%); IR: 3 029, 2 851, 1 645, 1 600, 1 454, 1 232, 1 014, 740 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.34 (s, 3H, $NCH_3$), 3.67 and 3.72 (AB quartet, 2H, $^2J_{HH}$ = 14.00 Hz, $CH_2$ of benzyl), 5.35 (s, 1H, CH), 6.42–6.51 (m, 2H, furan), 6.95–7.55 (m, 12H, CH of arom, vinylic group and furan); $^{13}$C NMR ($CDCl_3$) δ: 38.91 ($NCH_3$), 57.55 ($CH_2$ of benzyl), 58.46 (CH), 110.43, 110.53 and 143.05 (3 CH of furan), 109.64 and 138.14 (2 CH of vinylic), 116.69 (d, $^2J_{CF}$ = 22.01 Hz), 130.89 (d, $^4J_{CF}$ = 2.51 Hz), 129.35 (d, $^3J_{CF}$ = 8.17 Hz), 163.64 (d, $^1J_{CF}$ = 257.22 Hz), 127.35, 128.41 and 128.93 (5 CH of arom), 138.14 ($C_{ipso(C=C)}$ of $C_6H_5$), 148.71 ($C_{ipso(C=C)}$ of furan), 162.98 and 164.65 (2 C=N). Anal. calcd. for $C_{30}H_{27}N_3O_2$ (389.42): C, 70.94; H, 5.18; N, 10.79. Found: C, 70.97; H, 5.18; N, 10.80.

***N*-benzyl{5-[(*E*)-2-(4-chlorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}2-furyl-*N*-methylmethanamine (5n)**

Yellow oil, yield (88%); IR: 3 029, 2 851, 1 646, 1 593, 1 527, 1 454, 1 088, 1 013, 741 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.34 (s, 3H, $NCH_3$), 3.66 and 3.73 (AB quartet, 2H, $^2J_{HH}$ = 13.50 Hz, $CH_2$ of benzyl), 5.36 (s, 1H, CH), 6.42–6.51 (m, 2H, furan), 7.00–7.55 (m, 12H, CH of arom, vinylic group and furan); $^{13}$C NMR ($CDCl_3$) δ: 38.91 ($NCH_3$), 57.55 ($CH_2$ of benzyl), 58.47 (CH), 110.43, 110.54 and 143.06 (3 CH of furan), 127.36, 128.42, 128.68, 128.93 and 129.31 (9 CH of arom), 133.14 ($C_{ipso(C=C)}$ of $C_6H_4Cl$), 135.93 ($C_{Ar}$-Cl of $C_6H_4Cl$), 110.41 and 137.97 (2 CH of vinylic), 138.14 ($C_{ipso(C=C)}$ of $C_6H_5$), 148.68 ($C_{ipso(C=C)}$ of furan), 163.10 and 164.54 (2 C=N). Anal. calcd. for $C_{23}H_{20}ClN_3O_2$ (405.88): C, 68.06; H, 4.97; N, 10.35. Found: C, 68.09; H, 4.98; N, 10.37.

***N,N*-dibenzyl(2-furyl)[5-(2-phenyl-1-ethynyl)-1,3,4-oxadiazol-2-yl]methanamine (5o)**

Yellow oil, yield (91%); IR: 3 028, 2 845, 2 232, 1 600, 1 537, 1 454, 1 157, 1 014, 742 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 3.71 and 3.82 (AB quartet, 4 H, $^2J_{HH}$ = 13.76 Hz, 2 $CH_2$ of benzyl groups), 5.44 (s, 1H, CH), 6.43–6.52 (m, 2 H, furan), 7.24–7.68 (m, 16 H, CH of arom, vinylic group and furan); $^{13}$CvNMR ($CDCl_3$) δ: 53.87 (2 $CH_2$ of benzyl groups), 54.70 (CH), 72.98 and 97.29 (2 C

of C≡C), 110.42, 110.51 and 143.15 (3 CH of furan), 119.74, 138.58 and 139.30 (3 $C_{ipso(C=C)}$ of 3 $C_6H_5$), 127.34, 128.47, 128.71, 128.78, 130.72 and 132.40 (15 CH of arom), 148.63 ($C_{ipso(C=C)}$ of furan), 164.14 and 164.22 (2 C=N). Anal. calcd. for $C_{23}H_{20}ClN_3O_2$ (445.51): C, 78.18; H, 5.20; N, 9.43. Found: C, 78.20; H, 5.25; N, 9.44.

**N-benzyl(2-furyl)-N-methyl[5-(2-phenyl-1-ethynyl)-1,3,4-oxadiazol-2-yl]methanamine (5p)**

Yellow oil, yield (89%); IR: 3 028, 2 852, 2 232, 1 617, 1 537, 1 453, 1 157, 1 014, 741 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 2.34 (s, 3H, $NCH_3$), 3.65 and 3.72 (AB quartet, 2H, $^2J_{HH}$ = 13.50 Hz, $CH_2$ of benzyl), 5.37 (s, 1H, CH), 6.42–6.52 (m, 2H, furan), 7.30–7.66 (m, 11H, CH of arom and furan); $^{13}C$ NMR ($CDCl_3$) δ: 38.82 ($NCH_3$), 57.51 ($CH_2$ of benzyl), 58.48 (CH), 72.93 and 97.29 (2 C of C≡C), 110.45, 110.62 and 143.12 (3 CH of furan), 119.71 and 138.08 (2 $C_{ipso(C=C)}$ of 2 $C_6H_5$), 127.37, 128.44, 128.70, 128.90, 130.71 and 132.37 (10 CH of arom), 148.32 ($C_{ipso(C=C)}$ of furan), 163.99 and 164.12 (2 C=N). Anal. calcd. for $C_{23}H_{19}N_3O_2$ (369.42): C, 74.78; H, 5.18; N, 11.37. Found: C, 74.80; H, 5.20; N, 11.40.

**N-benzyl-N-ethyl-N-{2-furyl[5-(2-phenyl-1-ethynyl)-1,3,4-oxadiazol-2-yl]methyl}amine (5q)**

Yellow oil, yield (89%); IR: 3 028, 2 850, 2 232, 1 598, 1 537, 1 453, 1 157, 1 013, 740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 1.12 (t, 3H, $J$ = 7 Hz, $CH_3$ of Et), 2.53–2.79 (m, 2H, $CH_2$ of Et), 3.67 and 3.83 (AB quartet, 2H, $^2J_{HH}$ = 14 Hz, $CH_2$ of benzyl), 5.46 (s, 1H, CH), 6.40–6.48 (m, 2H, furan), 7.28–7.66 (m, 11H, CH of arom and furan); $^{13}C$ NMR ($CDCl_3$) δ: 13.21 ($CH_3$), 44.98 ($CH_2$, ethyl), 54.54 ($CH_2$ of benzyl group), 54.65 (CH), 72.98 and 97.19 (2 C of C≡C), 110.16, 110.40 and 142.94 (3 CH of furan), 119.74 and 139.00 (2 $C_{ipso(C=C)}$ of 2 $C_6H_5$), 127.14, 128.37, 128.63, 128.69, 130.69 and 132.37 (10 CH of arom), 148.95 ($C_{ipso(C=C)}$ of furan), 164.37 and 165.42 (2 C=N). Anal. calcd. for $C_{24}H_{21}N_3O_2$ (383.44): C, 75.18; H, 5.52; N, 10.96. Found: C, 75.20; H, 5.55; N, 11.00.

## CONCLUSIONS

To the best of our knowledge, this is the first report in which *N*-isocyaniminotriphenylphosphorane **4** is used in a four-component condensation in the presence of furfural and followed by an intramolecular *aza*-Wittig [50–52] ring closure of the iminophosphorane moiety with ester carbonyl. In conclusion, we reported a new MCR, yielding disubstituted 1,3,4-oxadiazoles, by using a sequence of multicomponent reactions and an intramolecular *aza*-Wittig closure. Due to the easy availability of the synthetic method and the neutral ring closure conditions, this new discussed synthetic method has the potential in synthesis of various disubstituted 1,3,4-oxadiazoles, which are of considerable interest as potential biologically active compounds or pharmaceuticals.

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## DIPAKEISTŲ 1,3,4-OKSADIAZOLŲ GAVIMAS IŠ FURFURALIO, KARBOKSIRŪGŠČIŲ IR ANTRINIŲ AMINŲ NAUDOJANT *N*-IZOCIANIMINOTRIFENIL-FOSFORANĄ

*Santrauka*

Pasiūlytas paprastas dipakeistų 1,3,4-oksadiazolų sintezės būdas naudojant *N*-izocianiminotrifenilfosforaną, antrinį aminą, karboksirūgštį ir furfuralį. Reakcija atliekama metileno chloride taikant Ugi-4CR/*aza*-Vitigo sintezės seką kambario temperatūroje, nenaudojant katalizatorių.