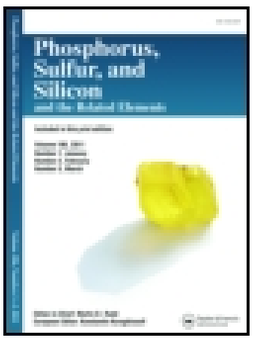

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THE REACTION OF *N*-ISOCYANIMINOTRIPHENYLPHOSPHORANE (NICITPP) WITH 2-OXOPROPYL-1-BENZENECARBOTHIOATE AND A PRIMARY AMINE IN THE PRESENCE OF BENZOIC ACID DERIVATIVES

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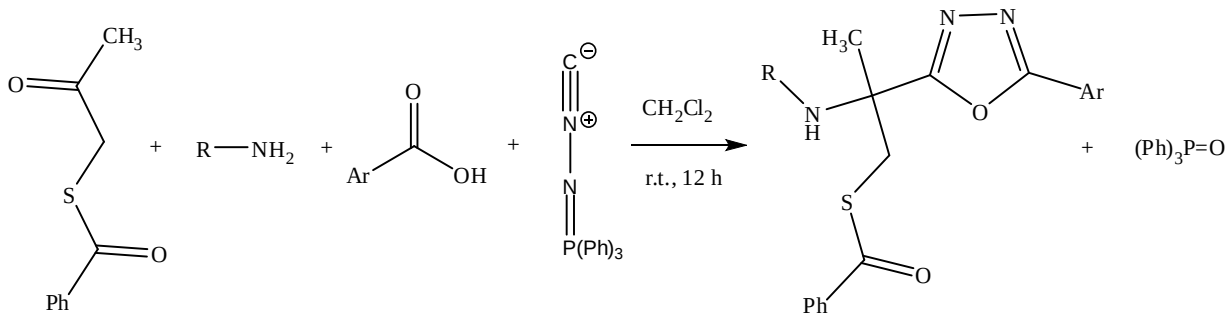
Abstract

Reactions of N-isocyaniminotriphenylphosphorane (NICITPP) with 2-oxopropyl-1-benzenecarbothioate in the presence of aromatic carboxylic acids and primary amines proceed smoothly at room temperature (18-26 °C) and in neutral conditions to afford sterically congested 1,3,4-oxadiazole derivatives in high yields. The reaction progresses smoothly and clearly under mild conditions and no side reactions were observed.



Keywords

N-isocyaniminotriphenylphosphorane (NICITPP); 2-oxopropyl-1-benzenecarbothioate; aromatic carboxylic acid; primary amine; 1,3,4-oxadiazole; *aza*-Wittig reaction

INTRODUCTION

Multicomponent reactions (MCR) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCR is also simple since all the organic reagents employed are consumed and are incorporated into the target compound.[1] MCR, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'druglike' molecules. The isocyanidebased MCR are especially important in this area.[2,3] Among the known multicomponent reactions to date, the most valuable reactions are those based on isocyanides. Isocyanide-based multicomponent reactions (abbreviated to IMCRs by Ugi and Domling) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry.[4,5]

During the past few decades, a great deal of effort has been made to develop methodologies that form carbon–sulfur bonds in the synthesis of molecules with various biological applications. Thioacids have little reactivity because of their low nucleophilic characteristic. But, the thioesters obtained from thioacids as nucleophiles are synthetically much valuable due to their widespread application in pharmaceutical chemistry and also they serve as key intermediates in the synthesis of various bioactive molecules. Meanwhile, thioesters are used as coupling partners in organometallic reactions, building blocks for the synthesis of heterocyclic compounds, and acyl transfer reactions.[6-16] Also, thioesters are multipurpose intermediates in natural products synthesis, which have multifarious applications in synthetic chemistry as precursors to aldehydes, ketones, acids, esters, lactones, amides, lactams, and heterocycles.[17,18]

Recently, the intramolecular version of the *aza*-Wittig-type reaction has attracted much attention because it has exhibited high potential for the synthesis of a wide variety of nitrogen heterocycles, which can be attributed to the rapid progress in the preparation of functionalized iminophosphoranes.[19] Existence of the nucleophilicity at the nitrogen is a factor of essential mechanistic importance by applying of these iminophosphoranes as *aza*-Wittig reagents. Iminophosphoranes are so important reagents in synthetic organic chemistry, in especial in the synthesis of naturally occurring products, compounds with biological and pharmacological activity.[19-21] In recent years, several synthetic methods have been reported for the preparation of *N*-isocyaniminotriphenylphosphorane (NICITPP) **6**.[22] There are several reports on the use of **6** in the synthesis of metal complexes.[22] Nevertheless, the organic chemistry of *N*-isocyaniminotriphenylphosphorane (NICITPP) **6** remains almost unexplored. *N*-Isocyaniminotriphenylphosphorane (NICITPP) **6** is expected to have synthetic potential because it makes a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality.[23] Recently, we have established a one-pot method for the synthesis of organophosphorus compounds.[24-28]

In recent years there has been considerable investigation on different classes of oxadiazoles.[29-35] In particular, compounds containing 1,3,4-oxadiazole nucleus have been shown to possess a wide range of pharmacological and therapeutic activities.[29-35] Some 2,5-disubstituted 1,3,4-oxadiazole derivatives have exhibited analgesic, anti-inflammatory, anticonvulsant, tranquilizing, myorelaxant, antidepressant, vasodilatatory, diuretic, antiulcer, antiarythmic, antiserotoninic, spasmolytic, hypotensive, antibronchocontrictive, anticholinergic, and antiemetic activities.[29-35] Furthermore, many 2,5-disubstituted 1,3,4-oxadiazole derivatives have been reported as active inhibitors of several enzymes.[29-35] As part of our ongoing program to develop efficient and robust methods for the synthesis of heterocyclic compounds,[36-45] we would like to report the preparation of a new class of 1,3,4-oxadiazole derivatives **7a-f** by a novel

four-component condensation reaction of 2-oxopropyl-1-benzenecarbothioate **3**, *N*-isocyaniminotriphenylphosphorane (NICITPP) **6**, primary amine **4** and aromatic carboxylic acid **5** in excellent yields under neutral conditions (Scheme 2).

RESULTS AND DISCUSSION

At first, we prepared the 2-oxopropyl-1-benzenecarbothioate **3** (Scheme 1);[46] and then we used it in the synthesis of 2-(arylamino)-2-(5-aryl-1,3,4-oxadiazol-2-yl)propyl-1-benzenecarbothioate derivatives **7** (Scheme 2). The 1:1 imine intermediate generated by the condensation reaction of primary amine **4** with 2-oxopropyl-1-benzenecarbothioate **3** is trapped by the *N*-isocyaniminotriphenylphosphorane (NICITPP) **6** in the presence of aromatic carboxylic acids **5** leads to the formation of 1,3,4-oxadiazole derivatives **7** and triphenylphosphine oxide **8** (Scheme 2). The reaction proceeds smoothly and cleanly under mild and neutral conditions and no side reactions were observed.

The structures of the products were deduced from their ^{1}H NMR, ^{13}C NMR, IR and Mass spectra. The ^{1}H NMR spectrum of **7a** consisted of a singlet for the CH_3 (δ= 1.76 ppm), a singlet for the NH (δ= 2.12 ppm, exchangeable by D_2O), a singlet for the CH_2 (δ= 3.74 ppm), ABq for the CH_2 (δ= 3.76 and δ= 3.84 ppm, $^{2}J_{HH}$ = 14.0 Hz), and multiplet for the aromatic protons (δ=7.20-7.96 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **7a** showed 19 distinct resonances, partial assignment of these resonances is given in the experimental section. The ^{1}H and ^{13}C NMR spectra of compounds **7b–f** were similar to those of **7a**, except for the aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

A mechanistic pathway for the reaction is provided in Scheme 3. On the basis of the chemistry of isocyanides, it is reasonable to assume that the first step may involve the formation of imine **9** by the condensation reaction of primary amine **4** with 2-oxopropyl-1-benzenecarbothioate **3**, the next step may

involve nucleophilic addition of the *N*-isocyaniminotriphenylphosphorane (NICITPP) **6** to the imine intermediate **9**, which facilitates by its protonation with the carboxylic acid **5**, leading to nitrilium intermediate **10**. This intermediate may be attacked by conjugate base of the carboxylic acid to form 1:1:1 adduct **11**. The intermediate **11** may undergo intramolecular *aza*-Wittig reaction[36–49] of iminophosphorane moiety with the ester carbonyl to afford the isolated sterically congested 1,3,4-oxadiazole derivatives **7** by removal of triphenylphosphine oxide **8** from intermediate **12**.

In summary, we think that the reported method offers a mild, simple, and efficient route for the preparation of sterically congested 1,3,4-oxadiazole derivatives **7** from 2-oxopropyl-1-benzenecarbothioate, *N*-isocyaniminotriphenylphosphorane (NICITPP) **6**, aromatic carboxylic acids and primary amines. Its ease of workup, high yields and fairly mild reaction conditions make it a useful addition to modern synthetic methodologies.

EXPERIMENTAL

General

N-Isocyaniminotriphenylphosphorane (NICITPP) **6** was prepared based on reported procedures.[22] 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 are TLC and NMR. TLC and NMR indicated that there is 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 ($CDCl_3$) were recorded on a BRUKER DRX-250 AVANCE

spectrometer at 250.0 and 62.5MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Preparative layer chromatography (PLC) plates were prepared from Merck silica gel (F_{254}) powder.

General Procedure for the Preparation of Compounds 7a-f

To a magnetically stirred solution of primary amine derivative (1 mmol; bezylamine, 0.107 g; 4-methylbenzylamine, 0.121 g; 4-methoxylbenzylamine, 0.137 g), 2-oxopropyl-1-benzenecarbothioate (1 mmol, 0.194 g) and *N*-isocyaniminotriphenylphosphorane (NICITPP) (1 mmol, 0.302 g) in CH_2Cl_2 (5 mL) was added dropwise a solution of aromatic carboxylic acid (1 mmol; 4-bromobenzoic acid, 0.201 g; 3-chlorobenzoic acid, 0.157 g; benzoic acid, 0.122 g; 4-chlorobenzoic acid, 0.157 g) in CH_2Cl_2 (5 mL) at room temperature (18-26 °C) over 15 min. The mixture was stirred at the same temperature (18-26 °C) for 12 h. The solvent was evaporated under reduced pressure, and the viscous residue was purified by preparative layer chromatography (PLC) plates (Merck silica gel (F_{254}) powder; petroleum ether-ethyl acetate (4:1). The characterization data of the compounds are given below.

2-(benzylamino)-2-[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]propyl1-benzenecarbothioate (7a).

White powder (yield 92%), m.p 95-97°C, ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 1.76 (s, 3H, CH_3), 2.12 (s, 1H, NH), 3.74 (s, 2H, CH_2), 3.76 and 3.84 (ABq, $^2J_{HH}$ = 14.0 Hz, 2H, CH_2), 7.20-7.96 (m, 14H, $CH_{arom,}$). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C (ppm) 23.21 (CH_3), 37.51, 47.98 ($2CH_2$), 56.94 (C-NH), 127.20, 127.39, 128.17, 128.37, 128.46, 128.64, 132.35, 133.64 (14CH), 122.73, 126.44, 136.54, 139.52 (4C), 164.43, 169.02 (2C=N), 190.52 (C=O). IR (KBr) ($\tilde{o}_{max}$, cm^{-1}): 3435, 2926, 2878,

1673, 1603, 1492, 1206, 1074, 909, 832, 731, 688. Ms m/z (%) 508 (4), 358 (64), 278 (20), 132 (24), 105 (96), 91 (100), 77 (68), 65 (20), 51 (28). Anal.Calcd for $C_{25}H_{22}BrN_3O_2S$ (508.43): C, 59.06; H, 4.36; N, 8.26. Found: C, 59.12; H, 4.30; N, 8.20.

2-(benzylamino)-2-[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl]propyl1-benzenecarbothioate (7b).

Yellow viscous oil (yield 88%), ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 1.80 (s, 3H, CH_3), 2.48 (s, 1H, NH), 3.77 (s, 2H, CH_2), 3.79 and 3.87 (ABq, $^2J_{HH}$ = 13.6 Hz, 2H, CH_2), 7.23-8.03 (m, 14H, $CH_{arom,}$). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C (ppm) 23.22 (CH_3), 37.55, 47.03 ($2CH_2$), 57.01 (C-NH), 125.12, 126.97, 127.27, 127.44, 128.24, 128.52, 128.70, 130.43, 131.83, 132.72 (14CH), 125.42, 135.18, 136.52, 139. 46 (4C), 164.06, 169.16 (2C=N), 190.56 (C=O). IR (KBr) ($\tilde{\delta}_{max}$, cm^{-1}): 3422, 3062, 2923, 1720, 1665, 1551, 1448, 1206, 910, 773, 688. Anal.Calcd for $C_{25}H_{22}ClN_3O_2S$ (463.11): C, 64.72; H, 4.78; N, 9.06. Found: C, 64.78; H, 4.85; N, 9.12.

2-(benzylamino)-2-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl1-benzenecarbothioate (7c).

Yellow viscous oil (yield 83%), ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 1.77 (s, 3H, CH_3), 2.80 (s, 1H, NH), 3.74 (s, 2H, CH_2), 3.77 and 3.86 (ABq, $^2J_{HH}$ = 13.7 Hz, 2H, CH_2), 7.28-8.05 (m, 15H, $CH_{arom,}$). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C (ppm) 23.22 (CH_3), 37.46, 48.04 ($2CH_2$), 56.99 (C-NH), 127.02, 127.25, 127.44, 128.27, 128.50, 128.67, 129.06, 131.80, 133.65 (15CH), 123.82, 136.61, 139.46 (3C), 165.20, 168.81 (2C=N), 190.64 (C=O). IR (KBr) ($\tilde{\delta}_{max}$, cm^{-1}): 3417, 2923, 2851, 1700, 1663, 1555, 1448, 1205, 909, 698. Anal.Calcd for $C_{25}H_{23}N_3O_2S$ (429.15): C, 69.91; H, 5.40; N, 9.78. Found: C, 69.84; H, 5.47; N, 9.71.

2-(benzylamino)-2-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]propyl1-benzenecarbothioate (7d).

Yellow viscous oil (yield 80%), ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 1.81 (s, 3H, CH_3), 2.15 (s, 1H, NH), 3.77 (s, 2H, CH_2), 3.79 and 3.87 (ABq, $^{2}J_{HH}$ = 13.6 Hz, 2H, CH_2), 7.21-8.01 (m, 14H, $CH_{arom,}$). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C (ppm) 23.23 (CH_3), 37.52, 48.01 ($2CH_2$), 56.97 (C-NH), 126.68, 127.24, 128.22, 128.50, 128.69, 129.43, 132.01, 133.70 (14CH), 122.28, 136.54, 138.05, 139.54 (4C), 164.38, 169.01 (2C=N), 190.58 (C=O). IR (KBr) ($\tilde{o}_{max}$, cm^{-1}): 3398, 3060, 1735, 1665, 1608, 1437, 1206, 910, 722, 691. Anal.Calcd for $C_{25}H_{22}ClN_3O_2S$ (463.11): C, 64.72; H, 4.78; N, 9.06. Found: C, 64.79; H, 4.71; N, 9.13.

2-[(4-methylbenzyl)amino]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl1-benzenecarbothioate (7e).

Yellow viscous oil (yield 75%), ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 1.75 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.32 (s, 1H, NH), 3.69 (s, 2H, CH_2), 3.76 and 3.84 (ABq, $^{2}J_{HH}$ = 13.7 Hz, 2H, CH_2), 7.05-8.03 (m, 14H, $CH_{arom,}$). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C (ppm) 21.00, 23.20 ($2CH_3$), 37.45, 47.74 (CH_2), 56.84 (C-NH), 126.96, 127.39, 128.14, 128.61, 128.97, 129.11, 131.75, 133.64 (14CH), 123.70, 136.61, 136.73, 136.86 (4C), 169.29 (2C=N), 193.65 (C=O). IR (KBr) ($\tilde{o}_{max}$, cm^{-1}): 3440, 2921, 2851, 1728, 1663, 1565, 1448, 1205, 910, 773, 688. Anal.Calcd for $C_{26}H_{25}N_3O_2S$ (443.17): C, 70.40; H, 5.68; N, 9.47. Found: C, 70.33; H, 5.75; N, 9.40.

2-[(4-methoxybenzyl)amino]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl1-benzenecarbothioate (7f).

Yellow viscous oil (yield 72%), ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 1.75 (s, 3H, CH_3), 2.16 (s, 1H, NH), 3.67 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.75 and 3.84 (ABq, $^{2}J_{HH}$ = 13.7 Hz, 2H, CH_2), 6.78-8.04 (m, 14H, $CH_{arom,}$). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C (ppm) 23.24 (CH_3), 37.44, 47.41 (CH_2), 55.20 (OCH_3), 56.82 (C-NH), 113.85, 126.96, 127.39, 128.61, 128.99, 129.38, 131.70, 133.56 (14CH), 120.85, 129.90, 136.67, 158.77 (4C), 168.34 (2C=N), 190.30 (C=O). IR (KBr) ($\tilde{o}_{max}$, cm^{-1}): 3436, 2926, 2875, 1675, 1604, 1532, 1448, 1240, 1032, 910, 822, 773, 688. Anal.Calcd for $C_{26}H_{25}N_3O_3S$ (459.16): C, 67.95; H, 5.48; N, 9.14. Found: C, 67.88; H, 5.41; N, 9.21.

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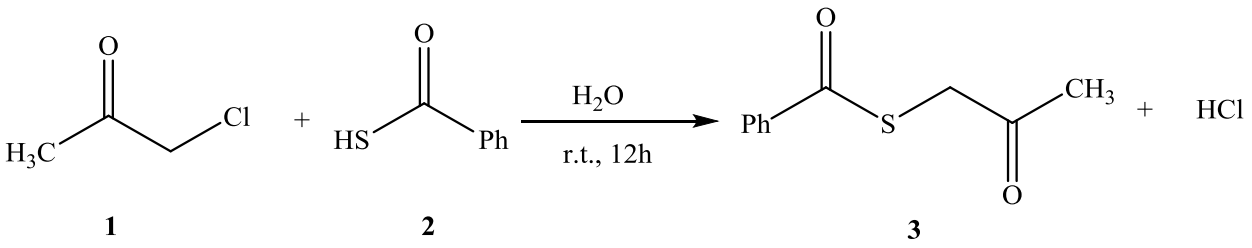
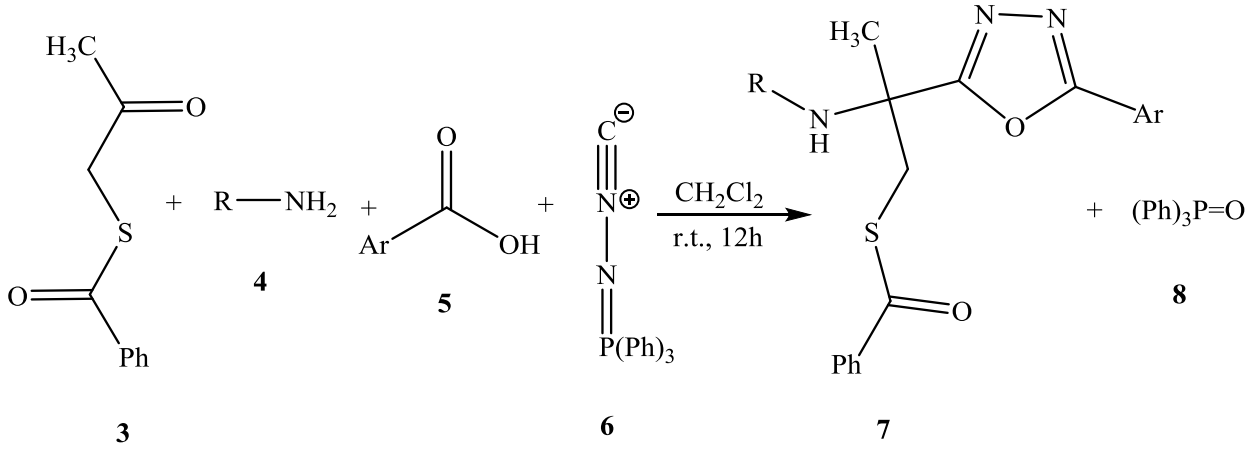


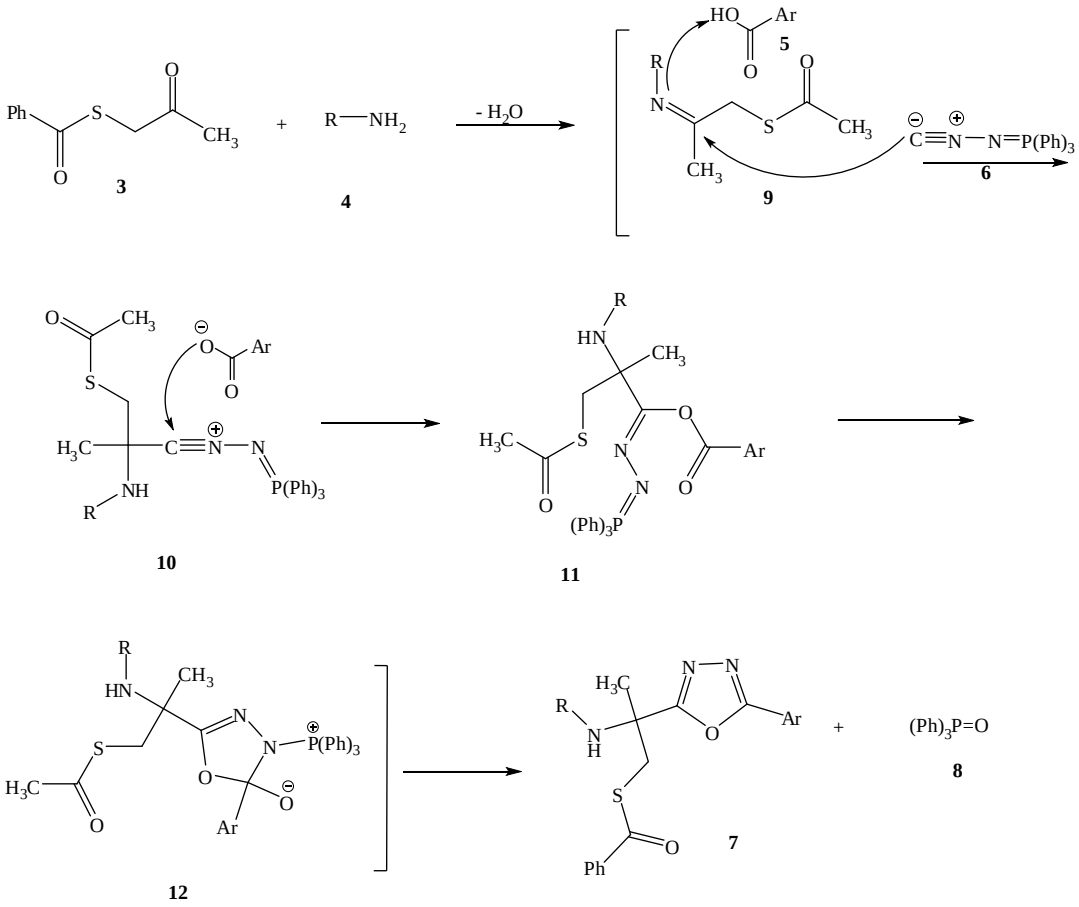
1 **2** **3**

Scheme 1. Synthesis of 2-oxopropyl-1-benzenecarbothioate **3** in water.



Scheme 2. Four-component synthesis of disubstituted 1,3,4-oxadiazole derivatives **7**

7a: R=benzyl, Ar=4-bromophenyl; **7b**: R=benzyl, Ar=3-chlorophenyl; **7c**: R=benzyl, Ar=phenyl; **7d**: R=benzyl, Ar=4-chlorophenyl; **7e**: R=4-methylbenzyl, Ar=phenyl; **7f**: R=4-methoxylbenzyl, Ar=phenyl.



Scheme 3. Proposed mechanism for the formation of sterically congested 2,5-disubstituted 1,3,4-oxadiazole derivatives **4**.