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Efficient one-pot, four-component synthesis of *N,N*-dibenzyl--1-(5-aryl-1,3,4-oxadiazol-2-yl)cyclobutylamine derivatives from the reaction of (isocyanoimino)triphenylphosphorane, dibenzylamine, an aromatic carboxylic acid and cyclobutanone

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Abstract: The four-component reaction of cyclobutanone, dibenzylamine and (isocyanoimino)triphenylphosphorane in the presence of aromatic carboxylic acids proceeds smoothly at room temperature under neutral conditions to afford *N,N*-dibenzyl-1-(5-aryl-1,3,4-oxadiazol-2-yl)cyclobutylamine derivatives in high yields.

Keywords: multicomponent reaction; isocyanide; 1,3,4-oxadiazole; heterocycles.

INTRODUCTION

There is increasing interest in the chemistry of heterocyclic compounds because of their vast distribution in natural compounds, their applications in pharmaceuticals, agrochemicals, and industrial chemicals, *etc*. 1,3,4-Oxadiazole derivatives are an important class of heterocycles, which possess pharmaceutical and biological activities, such as antimicrobial,[1-3] antimycobacterial,[4] anti-inflammatory,[5] anti-allergic,[6] antifungal and genotoxic activities.[7] Nowadays, many organic compounds can be synthesized in multicomponent reactions (MCRs).[8] An important class of MCRs are the isocyanide-based multicomponent reactions (IMCRs). IMCRs are especially interesting because they are more diverse and versatile than non-IMCRs.[9–18] Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multi-step in nature.[19–21] In recent years, a one-pot method for the synthesis of 1,3,4--oxadiazole derivatives from (isocyanoimino)triphenylphosphorane has been established.[22–26] In connection with interest in the synthesis of heterocycles,[27–30] the synthesis of *N,N*-dibenzyl-1-(5-aryl-1,3,4-oxadiazol-2-yl)cyclobutylamine derivatives *via* a four-component reaction of cyclobutanone, dibenzylamine, and

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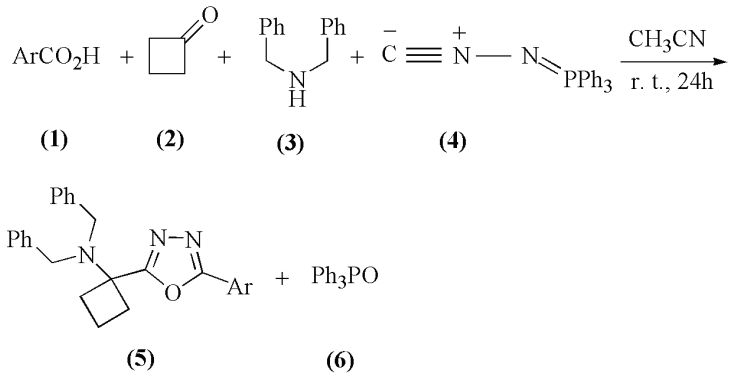
(isocyanoimino)triphenylphosphorane in the presence of aromatic carboxylic acids, in high yields and fairly mild reaction conditions, is reported herein (Scheme 1).



Scheme 1. Four-component reaction of carboxylic acids, cyclobutanone, dibenzylamine and (isocyanoimino)triphenylphosphorane.

RESULTS AND DISCUSSION

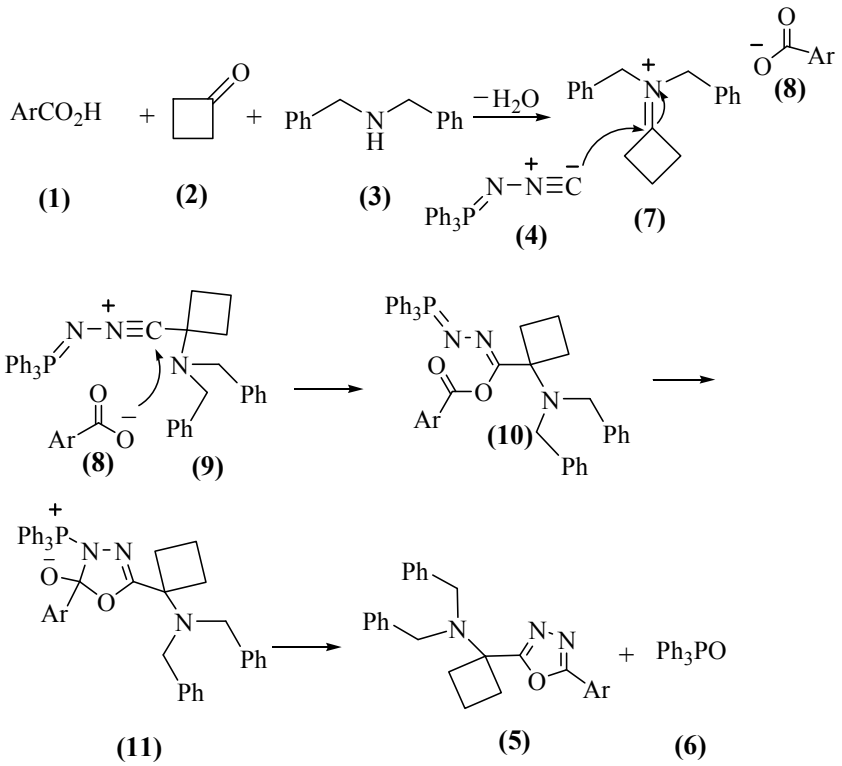
The four-component reactions of cyclobutanone (**2**), dibenzylamine (**3**) and (isocyanoimino)triphenylphosphorane (**4**) in the presence of aromatic carboxylic acids (**1**) led to *N*,*N*-dibenzyl-1-(5-aryl-1,3,4-oxadiazol-2-yl)cyclobutylamine derivatives (**5**) in high yields, under fairly mild reaction conditions (Scheme 1 and Table I). A mechanistic rationalization for this reaction is provided in Scheme 2. The imine intermediate generated by the reaction of cyclobutanone (**2**) and dibenzylamine (**3**) is protonated with aromatic carboxylic acid (**1**) to produce iminium intermediate (**7**). Nucleophilic addition of the (isocyanoimino)triphenylphosphorane (**4**) to the iminium ion (**7**) leads to a nitrilium intermediate (**9**). The intermediate **9** may be attacked by the carboxylate anion (**8**) to form adduct **10**. The adduct **10** may undergo an intramolecular aza-Wittig reaction of an iminophosphorane moiety with the ester carbonyl group to afford the 1,3,4-oxadiazole derivatives (**5**) by the removal of triphenylphosphine oxide (**6**) from intermediate (**11**).

The structures of the products were deduced from their ^{1}H-NMR, ^{13}C-NMR, mass, IR spectra, and elemental analysis. For example the ^{1}H-NMR spectrum of **5a** exhibited distinct signals at δ_H 1.71–1.92, 2.17–2.38 and 2.40–2.61 ppm (6H, 3*m*) arising from the $3CH_2$ groups of cyclobutane, δ_H 3.65 ppm (4H, *s*) from the $2CH_2$ groups of benzyl and at δ_H 7.12–8.18 ppm (15H, *m*) of the aromatic CH groups. The ^{13}C-NMR spectrum of **5a** showed 14 distinct resonances arising from the $3CH_2$ of cyclobutane (δ_c 14.47 and 33.05 ppm), the $2CH_2$ of benzyl (δ_c 53.85 ppm), C_{ipso} of cyclobutane (δ_c 62.66 ppm), aromatic carbons (δ_c 124.09, 126.88, 126.95, 128.01, 129.00, 129.12, 131.74 and 139.65 ppm), 2C=N (δ_c

165.47 and 168.55 ppm). The mass spectrum of **5a** displayed a molecular ion peak at *m/z* = 395. The analytic and spectral data for all the synthesized compounds are given in the Supplementary material to this paper.

TABLE I. Synthesis of *N,N*-dibenzyl-1-(5-aryl-1,3,4-oxadiazol-2-yl)cyclobutylamine derivatives

Entry	Ar	Product
1	C_6H_5	**5a**
2	2-Thienyl	**5b**
3	4-ClC_6H_4	**5c**
4	3-ClC_6H_4	**5d**
5	4-BrC_6H_4	**5e**
6	4-FC_6H_4	**5f**
7	4-MeC_6H_4	**5g**
8	3-MeC_6H_4	**5h**



Scheme 2. The proposed mechanism for the formation of **5**.

EXPERIMENTAL

The starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The melting points were measured

on an electrothermal 9100 apparatus and are uncorrected. The IR spectra were recorded on a Jasco FT-IR 6300 spectrometer. The ^{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. The mass spectra were recorded on a HP (Agilent Technologies) 5937 mass selective detector at an ionization potential of 70 eV. The elemental analyses were realized using a Heraeus CHN--O-rapid analyzer.

General procedure

To a magnetically stirred solution of cyclobutanone (**2**, 1 mmol), dibenzylamine (**3**, 1 mmol) and an aromatic carboxylic acid (**1**, 1 mmol) in CH_3CN (5 mL) was added dropwise a solution of (isocyanoimino)triphenylphosphorane (**4**, 1 mmol) in CH_3CN (5 mL) at room temperature over 15 min. The mixture was stirred for 24 h. The solvent was removed under reduced pressure and the viscous residue was purified by preparative layer chromatography (silica gel; petroleum ether–ethyl acetate (10:3)). The solvent was removed under reduced pressure and the products **5a**–**h** were obtained.

CONCLUSIONS

The reported method offers a mild, simple, and efficient route for the preparation of *N,N*-dibenzyl-1-(5-aryl-1,3,4-oxadiazol-2-yl)cyclobutylamine derivatives *via* a four-component reaction of cyclobutanone, dibenzylamine and (isocyanoimino)triphenylphosphorane in the presence of an aromatic carboxylic acid in high yields and under fairly mild reaction conditions.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

ЕФИКАСНА СИНТЕЗА ДЕРИВАТА *N*,*N*-ДИБЕНЗИЛ-1-(5-АРИЛ-1,3,4-ОКСАДИАЗОЛ-2-ИЛ)ЦИКЛОБУТИЛАМИНА У ЈЕДНОМ РЕАКЦИОНОМ КОРАКУ ЧЕТВОРОКОМПОНЕНТНЕ РЕАКЦИОНЕ СМЕШЕ – (ИЗОЦИЈАНОИМИНО)ТРИФЕНИЛФОСФОРАН, ДИБЕНЗИЛАМИН, АРОМАТИЧНА КАРБОКСИЛНА КИСЕЛИНА И ЦИКЛОБУТАНОН

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Реакциона смеша која садржи (изоцијаноимино)трифенилфосфоран, дибензиламин и циклобутанон, у присуству ароматичних карбоксилних киселина, при собној температури, као производ даје деривате *N*,*N*-дибензил-1-(5-арил-1,3,4-оксадиазол-2-ил)циклобутиламина у високом приносу.

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