One-Pot, Four-Component Synthesis of Fully Substituted 1,3,4-Oxadiazole Derivatives from (Isocyanoimino)triphenylphosphorane, a Primary Amine, an Aromatic Carboxylic Acid, and Chloroacetone

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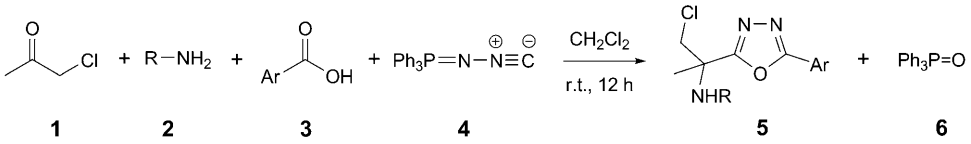
The 1:1 imine intermediate **7** generated by the addition of a primary amine **2** to chloroacetone (**1**) is trapped by (isocyanoimino)triphenylphosphorane (**4**) in the presence of an aromatic carboxylic acid **3** and leads to the formation of the corresponding iminophosphorane intermediate **9** (*Scheme 2*). The 1,3,4-oxadiazole derivatives **5** are then formed *via* an intramolecular aza-*Wittig* reaction of the iminophosphorane intermediate **9**. The reactions were completed under neutral conditions at room temperature. The fully substituted 1,3,4-oxadiazole derivatives **5** were produced in high yields (*Table*).

Introduction. – In recent years, several synthetic methods have been reported for the preparation of (isocyanoimino)triphenylphosphorane (= *N*-(triphenylphosphoranylidene)isocyanamide; CN–N=PPh$_3$; **4**) [1][2]. There are several reports on the use of **4** in the synthesis of metal complexes [1][2]. However, application of **4** in the synthesis of organic compounds is fairly rare [3–13]. As part of our ongoing program to develop efficient and robust methods for the preparation of organic compounds [14–28], we sought to develop a convenient preparation of fully substituted 1,3,4-oxadiazole derivatives **5a**–**5q**. Herein, we report a four-component reaction, which, starting from readily available chloroacetone (**1**), affords fully substituted 1,3,4-oxadiazole derivatives **5a**–**5q** (*Scheme 1*).

Scheme 1. *Four-Component Synthesis of 1,3,4-Oxadiazoles* **5** (see *Table*)



Results and Discussion. – The 1:1 imine intermediate (= *N*-alkylideneamine intermediate) generated by the condensation reaction of chloroacetone (**1**) with primary amines **2** is trapped by **4** in the presence of aromatic carboxylic acids **3** and leads to the formation of 1,3,4-oxadiazole derivatives **5** and Ph$_3$P=O (**6**; *Scheme 1* and *Table*). 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

Table. *Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazole Derivatives* **5a**–**5q** *from Chloroacetone* (**1**), *Primary Amine* **2**, *and Carboxylic Acid* **3** *in the Presence of (Isocyanoimino)triphenylphosphorane* (**4**)

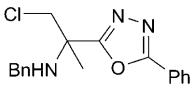
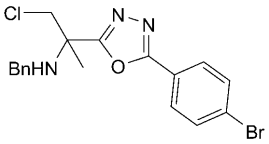
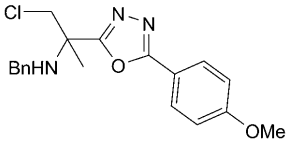
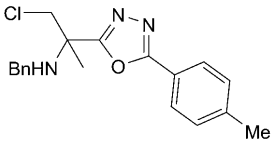
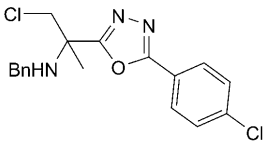
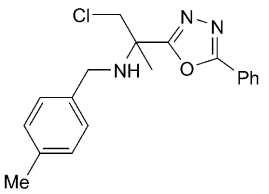
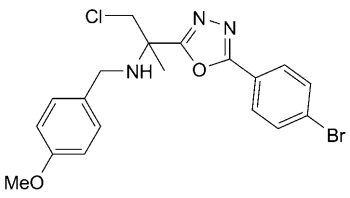
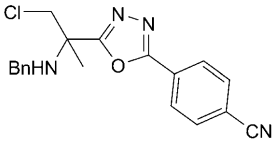
R	Ar	Product		Yield [%][a])	M.p. [°]	IR[b]) [cm^{-1}]
Bn	Ph		**5a**	85	82–84	1608, 1449
Bn	4-Br–C_6H_4		**5b**	87	99–101	1602, 1482
Bn	4-MeO–C_6H_4		**5c**	77	oil	1616, 1496
Bn	4-Me–C_6H_4		**5d**	78	70–72	1618, 1499
Bn	4-Cl–C_6H_4		**5e**	75	80–82	1608, 1486
4-Methyl-benzyl	Ph		**5f**	76	71–73	1609, 1449
4-Methoxy-benzyl	4-Br–C_6H_4		**5g**	75	95–97	1605, 1478
Bn	4-NC–C_6H_4		**5h**	75	oil	1656, 1494

Table (cont.)

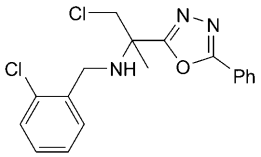
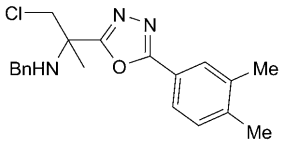
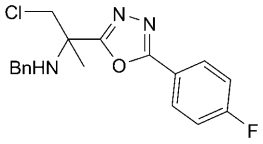
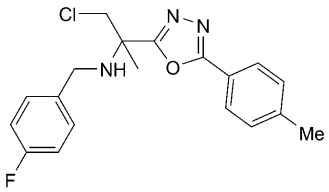
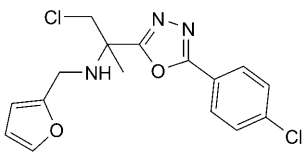
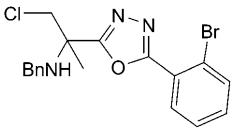
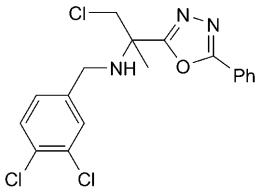
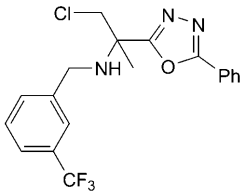
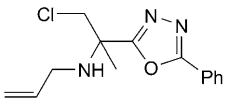
R	Ar	Product		Yield [%][a])	M.p. [°]	IR[b]) [cm^{-1}]
2-Chlorobenzyl	Ph		**5i**	82	65–67	1609, 1475
Bn	3,4-$Me_2C_6H_3$		**5j**	70	oil	1617, 1455
Bn	4-F–C_6H_4		**5k**	80	77–79	1612, 1499
4-Fluorobenzyl	4-Me–C_6H_4		**5l**	70	oil	1614, 1499
Furan-2-ylmethyl	4-Cl–C_6H_4		**5m**	80	79–81	1609, 1485
Bn	2-Br–C_6H_4		**5n**	86	oil	1602, 1455
3,4-Dichorobenzyl	Ph		**5o**	85	73–75	1612, 1471

Table (cont.)

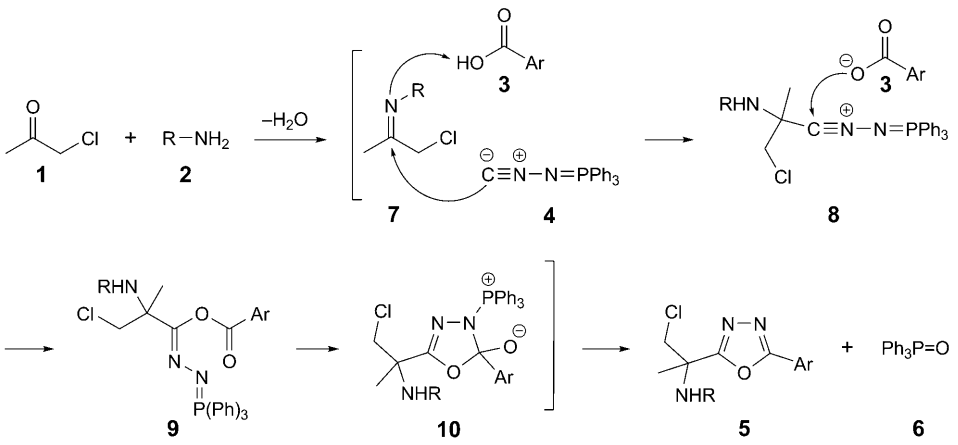
R	Ar	Product		Yield [%][a])	M.p. [°]	IR[b]) [cm^{-1}]
3-(Trifluoromethyl)-benzyl	Ph		**5p**	77	oil	1614, 1452
Allyl	Ph		**5q**	70	oil	1649, 1451

[a]) Yield of isolated **5**. [b]) Two main absorptions in KBr.

their IR, ^{1}H- and ^{13}C-NMR, and mass spectra. For example, the ^{1}H-NMR spectrum of **5a** consisted of an *AB* pattern for the H-atoms of the CH_2Cl group (δ(H) 3.69 and 3.75 (^2J(H,H) = 12.0 Hz)), and a second *AB* pattern for the H-atoms of the $PhCH_2$ group (δ(H) 3.96 and 4.07 (^2J(H,H) = 11.5 Hz)), a *s* for NH (δ(H) 2.22), and a *s* for Me (δ(H) 1.77). The Ar groups exhibited characteristic signals in the aromatic region of the spectrum. The ^{1}H-decoupled ^{13}C-NMR spectrum of **5a** showed 14 distinct signals; partial assignment of these signals is given in the *Exper. Part*. The ^{1}H- and ^{13}C-NMR spectra of compounds **5b**–**5q** were similar to those of **5a**, except for the aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

A mechanistic pathway for the reaction is provided in *Scheme 2*. On the basis of the chemistry of isocyanides, it is reasonable to assume that the first step may involve the

Scheme 2. *Proposed Mechanism for the Formation of Sterically Congested 1,3,4-Oxadiazole Derivatives* **5**



formation of imine **7** by the condensation reaction of chloroacetone (**1**) with the primary amine **2**. The next step may involve nucleophilic addition of (isocyanoimino)-triphenylphosphorane (**4**) to the imine intermediate **7**, which is facilitated by its protonation with the carboxylic acid **3**, leading to nitrilium intermediate **8**. This intermediate may be attacked by the conjugate base of the carboxylic acid to form the 1:1:1 adduct **9**. The intermediate **9** then undergoes an intramolecular aza-*Wittig* reaction [3–13] of the iminophosphorane moiety with the ester C=O group to afford the isolated sterically congested 1,3,4-oxadiazole derivative **5** by removal of $Ph_3P{=}O$ (**6**) from intermediate **10**.

We also used 1,1-dichloroacetone, 1,3-dichloroacetone, 2-chloroacetophenone, 2-bromoacetophenone, trifluoroacetone, and 2,2-dichlorobutyrophenone instead of chloroacetone **1** in this reaction, but no corresponding products **5** were observed. In all the cases, several colored products were detected by TLC monitoring.

Conclusions. – We believe that the reported method offers a mild, simple, and efficient route for the preparation of fully substituted 1,3,4-oxadiazol derivatives of type **5**. Ease of workup, high yields, and fairly mild reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this synthetic process are under investigation.

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Experimental Part

General. (Isocyanoimino)triphenylphosphorane (= *N*-triphenylphosphoranylidene)isocyanamide; **4**) was prepared based on reported procedures [1][2]. Other starting materials and solvents were obtained from *Merck* (Germany) and *Fluka* (Switzerland) and were used without further purification. Reaction monitoring by TLC and NMR (no by-products formed). Prep. TLC: plates coated with *Merck* silica gel F_{254} powder. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Jasco-6300* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra ($CDCl_3$): *Bruker-DRX-250-Avance* spectrometer; at 250.0 and 62.5 MHz, resp.; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan-Matt-8430* mass spectrometer operating at an ionization potential of 20 eV; in *m*/*z* (rel. %). Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

General Procedure. To a magnetically stirred soln. of primary amine **2** (1 mmol), chloroacetone (**1**; 1 mmol), and (isocyanoimino)triphenylphosphorane (**4**; 1 mmol) in CH_2Cl_2 (5 ml) was added dropwise a soln. of benzoic acid derivative **3** (1 mmol) in CH_2Cl_2 (5 ml) at r.t. over 15 min. The mixture was stirred for 12 h. The solvent was evaporated and the viscous residue purified by prep. TLC (silica gel F_{254}, petroleum ether/AcOEt 4:1). Purified **5a**–**5q** were obtained as yellow powders or yellow oils. For yields, m.p., and IR of **5a**–**5q**, see *Table*[1]).

N-*Benzyl*-N-*[2-chloro-1-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amine* (= *α-(Chloromethyl)-α-methyl-5-phenyl*-N-*(phenylmethyl)-1,3,4-oxadiazol-2-methanamine*; **5a**): Yellow powder. IR (KBr): 3456, 3269, 2927, 1608, 1449, 1069. ^1H-NMR ($CDCl_3$): 1.77 (*s*, Me); 2.23 (*s*, NH); 3.69, 3.76 (*AB*, $^2J = 12.3$, CH_2Cl); 3.96, 4.07 (*AB*, $^2J = 11.5$, PhCH_2); 7.24–8.07 (*m*, 10 arom H). ^{13}C-NMR ($CDCl_3$): 22.53 (Me); 47.82, 50.24. (2 CH_2); 57.58 (CNH); 127.00, 127.31, 128.27, 128.51, 129.07, 131.8 (10 CH); 123.70, 139.33 (2 C); 165.24, 167.77 (2 C=N). EI-MS: 327 (M^+), 187 (16), 149 (33), 105 (70), 91 (100), 76 (29), 43 (54). Anal. calc. for $C_{18}H_{18}ClN_3O$ (327.81): C 65.95, H 5.53, N 12.82; found: C 65.83, H 5.49 N 12.77.

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[1]) Supplementary material (characterization data of **5b**–**5q**) may be obtained upon request from the senior author *A. R*

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