Synthesis of 1,3,4-Oxadiazoles from Carboxylic Hydrazides and of 1,2-Oxazin-6-ones from α-(Hydroxyimino)carboxylic Esters with Keteneylidene Triphenylphosphorane

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Abstract: In a one-pot procedure 1,3,4-oxadiazoles **8** are prepared from carboxylic hydrazides **2** and keteneylidene triphenylphosphorane **1** *via* an untypical *inter*molecular Wittig olefination of a carbamate type carbonyl group. Under similar conditions, reaction of **1** and α-(hydroxyimino) carboxylic esters **9** furnishes 1,2-oxazin-6-ones **11** by a different process including an *intra*molecular olefination step.

Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical and technical interest, which is documented by a steadily increasing number of publications and patents. For instance, the leprostatic Vadrin®[1] or the hypnotic Eudormil®[2] are well established pharmaceuticals of this type. Some technical applications of 1,3,4-oxadiazole derivatives lie in the fields of photosensitizers[3] and liquid crystals.[4]

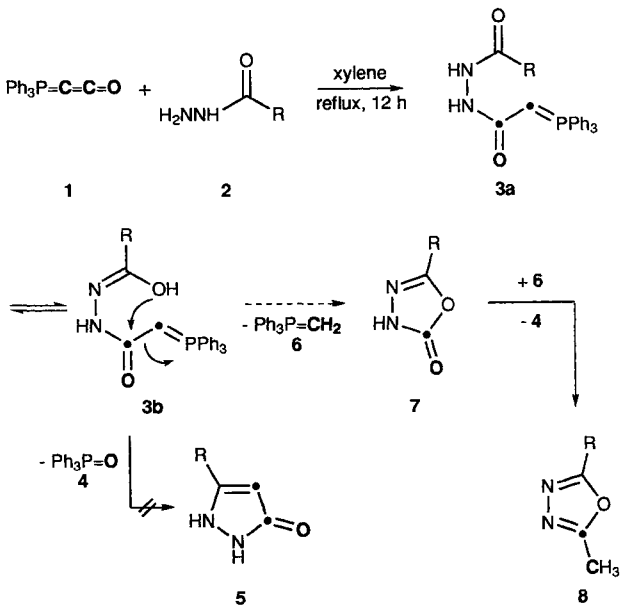
The common synthetic approaches to oxadiazoles start from acyclic compounds with preformed C-O-N-N skeletons (for example carboxylic hydrazides) which are then reacted with suitable C-1 building blocks like phosgene.[5] An alternative route is the ring conversion of tetrazoles.[6] We now found a new shortcut path to 5-methyl-1,3,4-oxadiazoles **8** by reaction of carboxylic hydrazides **2**[7] with keteneylidene triphenylphosphorane **1**[8] in refluxing xylene, where the methyl group has not to be introduced separately but is formed straight away by a Wittig olefination step. Compound **1** itself can be easily prepared by the mole and stored under ambient atmosphere for months.

The reaction is likely to commence with addition of the NH_2-group of **2** to the C=C bond of **1** to give the acyl ylide **3**, which does not undergo a subsequent intramolecular Wittig olefination to **5** – a pattern we have otherwise used extensively for the construction of 5- to 7-membered heterocycles like tetronates or azepinones from the corresponding OH-, SH- or NH_2-functionalized carboxylic esters.[9] Instead, **3** cyclizes to **7** with concomitant elimination of methylene triphenylphosphorane **6** – a reaction mode that we have already observed and elucidated for the formation of 2-oxazolones from **1** and α-hydroxy amides.[10] Ylide **6** then undergoes an unusual *inter*molecular Wittig reaction with the carbamate type carbonyl group of **7** (carbamates are normally resistant to phosphorus ylides) to give 5-methyl-1,3,4-oxadiazoles **8** (Scheme 1, Table 1).

A lot of reactions are known to further functionalize the oxadiazole core[11] to which our method could provide an easy entry. It is not applicable to hydroxamic acids, which give rise to acid-catalyzed dimerization of ylide **1**, nor to primary hydrazones[12] of α-keto esters. These do not furnish the corresponding dihydropyridazines but undergo a Wolff–Kishner like reaction instead, yielding merely the respective parent hydrocarbons, albeit in good yields and under comparably mild conditions.[13]

However, α-(hydroxyimino)carboxylic esters[15] like **9** – i.e. the oximes of α-keto esters – give a clean reaction with **1** yielding the corresponding 1,2-oxazin-6-ones **11** *via* the more common two-step process of addition – leading to **10** – and subsequent *intra*molecular Wittig olefination. The heterocycles **11** are the first examples of non-annulated six-membered lactones prepared by reaction of **1** with derivatives of carboxylic esters. Satisfactory yields could only be obtained for 3-arylsubstituted products, so far. Further work is in progress to widen the scope of this reaction (Scheme 2, Table 2).

1,2-Oxazines are basically interesting intermediates in the synthesis of differently substituted pyrroles by base-promoted ring contraction reactions.[16, 17] Alternative synthetic approaches comprise ring expansion reactions of furanones with NH_2OSO_3H[18] or cyclization reactions of monooximes of α-,β-unsaturated 1,4-dicarbonyl compounds.[19]



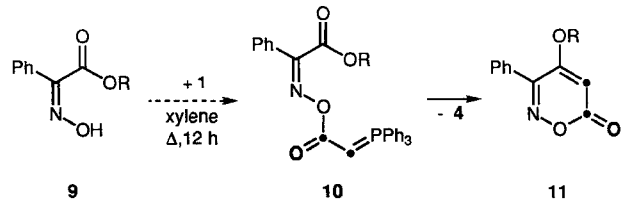
1 2 3a 3b 7 5 8

Scheme 1

Table 1. 5-Methyl-1,3,4-oxadiazoles **8** from **1** and hydrazides **2**

8	R	bp (°C/Torr)	Yield (%)
a	Me	50/12[a]	88
b	i-Pr	100-105/12	60
c	n-Bu	85-90/12	50
d	Ph	[b]	50
e	CH_2Ph	- -	45

[a] loc. cit. ref. 14: 178 °C/760; [b] mp 67°C



9 10 11

Scheme 2

Table 2. 4-Alkoxy-3-phenyl-1,2-oxazin-6-ones **11** from **1** and oximes **9**

11	R	mp (°C)	Yield (%)
a	Et	85	45
b	i-Pr	106	51
c	*cyc*-C_6H_{11}	128	41
d	CH_2Ph	134	46

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(20) *Synthesis of 1,3,4-oxadiazoles* **8** *from hydrazides* **2**,[7] and of *1,2-oxazin-6-ones* **11** *from oximes*[15]. – *General procedure:* A solution of 8.0 mmol of either **2** or **9**, respectively, 3.02 g (10.0 mmol) of keteneylidene triphenylphosphorane **1**, and catalytic amounts of benzoic acid in 70 ml of xylene was refluxed for 12 h. For the syntheses of **8a-c** THF was used as solvent and the mixture was heated to 140 °C in a sealed glass tube for 12 h. The solvent was then evaporated and the residue chromatographed over silica gel with diethyl ether / *n*-pentane. Compounds **8a-c** were directly distilled from the residue.
Selected data:
2-Isopropyl-5-methyl-1,3,4-oxadiazole **8b**
605 mg (4.8 mmol, 60%) as colourless oil from 815 mg (8.0 mmol) of isobutyric hydrazide, bp 100-105 °C/12; calcd. for $C_6H_{10}N_2O$: C, 64.22; H, 9.00; N, 24.97. Found: C, 64.22; H, 8.94; N, 24.95; IR (neat) ν = 2970, 2950, 2930, 1580, 1550, 1140 cm^{-1}; ^{1}H-NMR δ 1.38 (d, 6H, *J* = 6.8 Hz, 2 CH_3), 2.51 (s, 3H, CH_3), 3.12-3.19 (m, 1H, CH); ^{13}C-NMR δ 11.0, 20.0 (CH_3), 26.3 (CH), 163.5, 171.1 (C); MS (70 eV), *m/z* (%) = 126 (35) [M^+], 111 (70) [M^+-CH_3], 83 (20) [M^+-$CH(CH_3)_2$], 43 (100) [$CH(CH_3)_2$+].
4-Isopropyloxy-3-phenyl-6H-1,2-oxazin-2-one **11b**
945 mg (4.1 mmol, 51%) as brown solid from 1.77 g (8.0 mmol) of isopropyl 2-phenyl-2-hydroxyimino acetate, mp 106 °C, eluted with diethyl ether/*n* -pentane (4:1); calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.67; N, 6.06. Found: C, 67.59; H, 5.59; N, 6.08; IR (CH_2Cl_2) : ν = 3040, 1720, 1610, 1380, 1260, 1100 cm^{-1}; ^{1}H-NMR δ 1.39 (d, 6H, *J* = 6.1 Hz, 2 CH_3), 4.61-4.67 (m, 1H, CH), 5.89 (s, 1H, 5-H), 7.44-7.62 (m, 5H, ArH); ^{13}C-NMR δ 21.0 (CH_3), 73.5, 96.6 (CH), 128.3, 129.4 (ArCH), 129.5 (C), 130.5 (ArCH), 153.7, 156.9, 166.0 (C); MS (70 eV), *m/z* (%) = 231 (100) [M^+], 189 (60) [M^+-$C(CH_3)_2$], 172 (5) [M_+-$OCH(CH_3)_2$], 104 (80) [$PhCNH^+$].