Efficient, High-Yield, One-Pot Protocol for the Synthesis of 1,2,4-Oxadiazine Derivatives

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Abstract: 1,2-Diaza-1,3-dienes easily react as Michael acceptors with arylamidoximes in a one-pot, high-yield heterocyclization process. Depending on the linear or cyclic structure of the ene mojety, 1,2,4-oxadiazin-5-ones or spiro cycloalkyl-1,2,4-oxadiazin-5-one derivatives can be directly obtained.

Key words: 1,2-diaza-1,3-dienes, arylamidoximes, nucleophilic additions, cyclizations, spiro compounds

The development of general and simple synthetic pathways for the generation of new and original libraries of heterocyclic compounds is currently one of the most important challenges in organic chemistry. A literature survey revealed that oxadiazine derivatives possess quite interesting pharmacological properties[1] and other biological activities.[2]

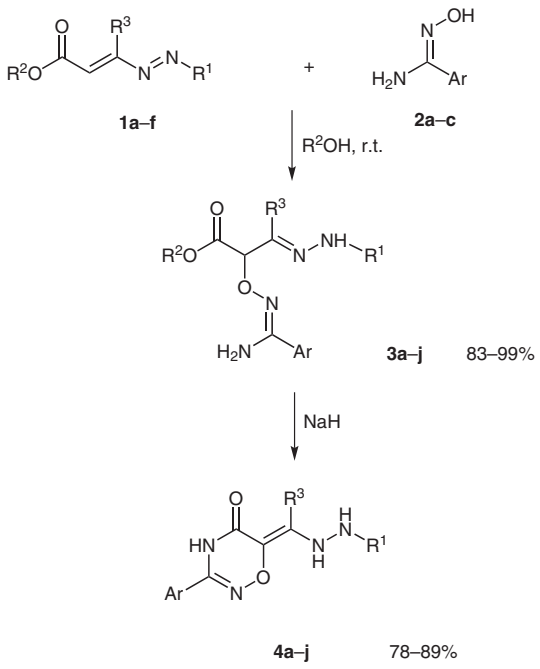
Although the use of amidoximes[3] as building blocks in 1,2,4-oxadiazole synthesis from different substrates is well documented,[4] their use to produce 1,2,4-oxadiazine derivatives is scarcely represented,[5a–d] especially by reaction with activated α,β-unsaturated systems.[5e]

Based on our experience concerning the construction of useful heterocyclic scaffolds from 1,2-diaza-1,3-dienes,[6] we wanted to approach a straightforward method for acquiring the title compounds.

Conjugated heterodiene system enhances the electrophilic character of the terminal carbon of 1,2-diaza-1,3-dienes making it capable of undergoing nucleophilic attack. Since arylamidoximes possess both a hydroxyimino and an amino group at the same carbon atom, they appeared to be the appropriate for the construction of oxadiazine ring.

Initially, we investigated the reactivity between 1,2-diaza-1,3-butadienes **1a–f** and arylamidoximes **2a–c** in nonpolar and polar solvents (toluene, THF, MeCN, DMF, MeOH). In every case, the reaction was fast and proceeded through a regioselective O-nucleophilic attack of the amidoxime derivative at terminal carbon of the conjugated azo–ene system allowing to produce stable Michael adducts **3a–j** in nearly quantitative yields (83–99%; Scheme 1, Table 1). In principle and according to our previous similar study,[7] under basic conditions the amidine function could provide different intramolecular ring closures: one at the ester function bonded at C4, the other at the hydrazono function.

It was found that the treatment of **3a–j** in THF with a stoichiometric amount of NaH promoted regioselective intramolecular cyclization at the ester function with loss of an alcohol molecule affording 1,2,4-oxadiazin-5-one derivatives **4a–j** in moderate yields.



Scheme 1

Based on these observations and with the aim of developing a one-pot protocol for these heterocyclic compounds,[8] we decided to carry out the reactions between **1a–f** and **2a–c**, firstly in the appropriate alcohol until formation of **3a–j**[9] and then by adding NaH to promote the ring closure. This tandem Michael addition–heterocyclization process, followed by acidic workup, exclusively provided new widely functionalized 1,2,4-oxadiazin-5-one derivatives **4a–j**[10] in excellent yields (78–89%; Table 1). To the best of our knowledge, only one report exists for similar com-

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Table 1 Results of the Synthesis of Michael Adducts **3a–j** and 1,2,4-Oxadiazin-5-one Derivatives **4a–j**

Entry	1,2-Diaza-1,3-butadiene **1**				Arylamidoxime **2**		Michael adduct **3**			
	1	R^1	R^2	R^3	**2**	Ar	**3**	Yield (%)[a]	**4**	Yield (%)[b]
1	**1a**	CO_2Me	Me	Me	**2a**	4-MeC_6H_4	**3a**	92	**4a**	87
2	**1b**	CO_2t-Bu	Me	Me	**2a**	4-MeC_6H_4	**3b**	95	**4b**	86
3	**1c**	4-$O_2NC_6H_4$	Me	Me	**2a**	4-MeC_6H_4	**3c**	90	**4c**	85
4	**1d**	CO_2Et	Et	Me	**2b**	4-t-BuC_6H_4	**3d**	83	**4d**	78
5	**1e**	CO_2Bn	Me	Me	**2b**	4-t-BuC_6H_4	**3e**	97	**4e**	88
6	**1a**	CO_2Me	Me	Me	**2c**	Ph	**3f**	99	**4f**	84
7	**1b**	CO_2t-Bu	Me	Me	**2c**	Ph	**3g**	83	**4g**	89
8	**1d**	CO_2Et	Et	Me	**2c**	Ph	**3h**	98	**4h**	81
9	**1e**	CO_2Bn	Me	Me	**2c**	Ph	**3i**	93	**4i**	79
10	**1f**	CO_2t-Bu	Me	Et	**2c**	Ph	**3j**	95	**4j**	86

[a] Yield of pure isolated adduct.
[b] Yield of pure isolated product in one-pot procedure.

pounds, prepared by Santilli who used dimethyl acetylenedicarboxylate as activated unsaturated system.[5e]

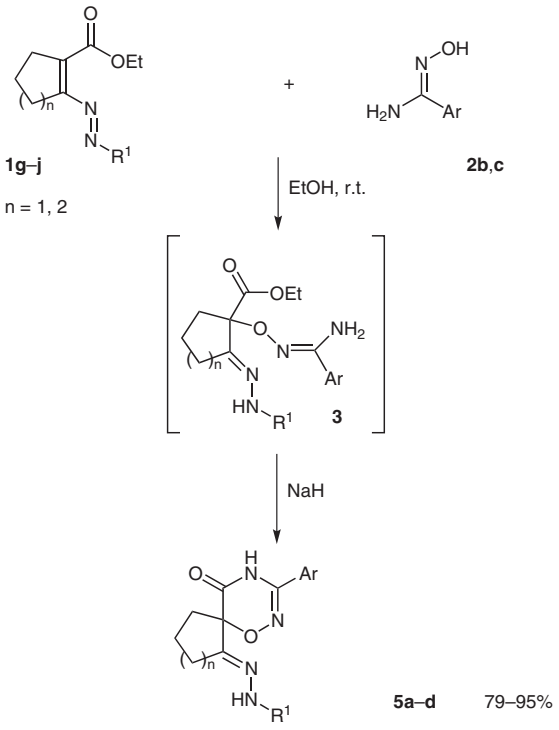
With optimized conditions in hand, a variety of cyclic conjugated azoalkenes was used to establish the generality and efficiency of this protocol. Cycloalkenyl-1-diazenes **1g–j**[11] readily reacted with arylamidoximes **2b**,**c** in ethanol at room temperature to produce hydrazone derivatives **3**. These were not isolated but were immediately treated with NaH to give the subsequent [4+2] heterocyclization process (Scheme 2, Table 2). After evaporation of the reaction solvent and subsequent acidic workup,[12] novel spirocycloalkyl-1,2,4-oxadiazin-5-one derivatives **5a–d**[13] were obtained. In agreement with the above previous results and in contrast with results with similar reactive systems,[14] internal nucleophilic attack by means of the amidino function took place exclusively at the ethoxycarbonyl group at C4 of cycloalkyldiazenes **1g–j**.

Table 2 Synthesis of Spiro Cycloalkenyl-1,2,4-Oxadiazine Derivatives **5a–d**

Entry	Cycloalkenyl-1-diazene **1**			Arylamidoxime **2**		Spiro **5**	
	1	R^1	n	**2**	Ar	**5**	Yield (%)[a]
11	**1g**	CO_2Me	1	**2b**	4-t-BuC_6H_4	**5a**	79
12	**1h**	CO_2Me	2	**2c**	Ph	**5b**	95
13	**1i**	CONHPh	2	**2c**	Ph	**5c**	92
14	**1j**	CO_2Bn	2	**2c**	Ph	**5d**	85

[a] Yield of pure isolated product in one-pot procedure.

In summary, we have reported an easy and efficient one-pot synthesis of a set of widely functionalized 1,2,4-oxadiazin-5-one derivatives by coupling arylamidoximes with 1,2-diaza-1,3-dienes as activated olefinic systems.



Scheme 2

One of the most interesting features of the methodology presented here is that there is no need to isolate Michael adducts, therefore constituting a practical, high-yielding, one-pot protocol for the formation of 1,2,4-oxadiazin-5-one derivatives variously functionalized at C6 of the six-membered heterocycle giving materials potentially useful as plant hormones and herbicides.[15]

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(8) **One-Pot Procedure for the Preparation of 1,2-Diaza-1,3-butadiene Derivatives 4a–j**
1,2-Diazabuta-1,3-diene **1a–f** (1 mmol), prepared and used as a *EE*/*EZ*-isomer mixture,[6a] and arylamidoxime **2a–c** (1 mmol) were dissolved in alcohol (8 mL) with magnetic stirring, and the reaction mixture was allowed to stand at r.t. until disappearance of the reagents and the formation of Michael adduct **3a–j** (0.33–4.0 h, monitored by SiO_2 TLC). A stoichiometric amount of NaH was added, and the crude reaction mixture was allowed to stand at r.t. until the complete disappearance of **3a–j** was observed by TLC analysis (0.5–8.0 h). After removal of the solvent in vacuo, the residue was suspended in H_2O, neutralized with 2 N HCl, extracted with CH_2Cl_2, and the organic extracts dried. After filtering, the organic solvent was evaporated, and the solid residue was crystallized from the appropriate solvent.

(9) **Data for Michael Adduct 3f**
White powder from EtOAc–*n*-pentane, mp 99–100 °C (dec.). IR (KBr): 3490, 3395, 2995, 1765, 1730, 1700, 1640, 1590, 1545 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.91 (s, 3 H, CH_3), 3.67 (s, 6 H, 2 × OCH_3), 4.98 (s, 1 H, CH), 6.29 (s, 2 H, NH_2), 7.36–7.43 (m, 3 H, Ar), 7.61 (d, *J* = 8.0 Hz, 2 H, Ar), 10.15 (s, 1 H, NH). ^{13}C NMR (100 MHz DMSO-d_6): δ = 12.90, 51.86, 51.93, 84.33, 126.08, 128.20, 129.72, 132.07, 148.14, 152.82, 154.46, 169.25. MS: *m/z* (%) = 322 [M^+] (0.6), 291 (0.5), 263 (1), 249 (1), 136 (15), 115 (58), 83 (100). Anal. Calcd for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.73; H, 5.61; N, 13.62.

(10) **Data for Methyl 2-[1-(5-Oxo-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-6-yliden)ethyl]-1-hydrazinecarboxylate (4f)**
Pink powder from CH_2Cl_2–PE (40–60 °C), mp 148–149 °C (dec.). IR (KBr): 3420, 3390, 3320, 2990, 1770, 1740, 1620, 1575 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.97 (s, 3 H, CH_3), 3.61 (s, 3 H, OCH_3), 6.88 (br s, 1 H, NH), 7.52–7.63 (m, 3 H, Ar), 7.98 (d, *J* = 6.8 Hz, 2 H, Ar), 9.93 (br s, 1 H, NH), 11.43 (br s, 1 H, NH). ^{13}C NMR (100 MHz DMSO-d_6): δ = 12.12, 51.81, 93.61, 127.25, 128.30, 128.85, 132.48, 152.38, 154.36, 160.94, 181.72. ESI-MS: *m/z* calcd for $C_{13}H_{14}N_4O_4$: 290.1; found: 291 [M+1].

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(12) **Typical One-Pot Procedure for the Synthesis of Spirocycloalkyl-1,2,4-oxadiazin-5-one Derivatives 5a–d**
To a solution of arylamidoxime **2b**,**c** (1 mmol) in EtOH (4 mL), 1-cycloalkenyl-1-diazene **1g–j** (1 mmol), prepared as previously reported and dissolved in EtOH (4 mL), was added dropwise at r.t. with magnetic stirring. The reaction mixture was allowed to stand at r.t. until the disappearance of the reactants (0.5–6.0 h) and the formation of the pertinent 1,4-adduct **3**. The crude reaction mixture was then treated with NaH (1 equiv) until complete disappearance of the intermediate was observed by TLC analysis (0.5–4.0 h). After removal of the solvent in vacuo, the residue was suspended in H_2O, neutralized with 2 N HCl, extracted with CH_2Cl_2, and the organic extracts dried. After filtering, the organic solvent was evaporated and the solid residue was crystallized from the appropriate solvent.

(13) **Data for Methyl 2-{12-Oxo-9-phenyl-7-oxa-8,11-diazaspiro[5.6]dodec-8-en-1-yliden}-1-hydrazinecarboxylate (5b)**
White powder from THF–*n*-pentane, mp 218–219 °C (dec.). IR (Nujol): 3368, 3187, 1749, 1713, 1616 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.34–1.40 (m, 1 H, cy), 1.66–1.99 (m, 5 H, cy), 2.19–2.27 (m, 1 H, cy), 2.90–2.94 (m, 1 H,

cy), 3.62 (s, 3 H, OCH_3), 7.44–7.51 (m, 3 H, Ar), 7.65 (d, J = 6.8 Hz, 2 H, Ar), 10.23 (s, 1 H, NH), 11.28 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.83, 22.97, 24.75, 31.24, 51.87, 79.43, 127.19, 128.47, 129.44, 131.03, 150.26, 153.64, 154.41, 167.10. ESI-MS: *m/z* calcd for $C_{16}H_{18}N_4O_4$: 330.1; found: 331 [M + 1].

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