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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1479–1483

A versatile solid-phase synthesis of 3-aryl-1,2,4-oxadiazolones and analogues

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Received 5 November 2006; revised 8 December 2006; accepted 12 December 2006
Available online 16 January 2007

Abstract—We report here the first method to load acidic heterocyclic compounds (1,2,4-oxadiazol-5-one, 1,2,4-oxadiazol-5-thione and 1,2,3,5-oxathiadazol-2-oxide) on a polymer. Using Mitsunobu conditions, these heterocycles were anchored on a 4-hydroxymethyl-3-methoxyphenoxybutyric acid benzhydrylamine (HMPB-BHA) resin. After diversification, compounds can be recovered by a simple treatment in diluted TFA. To illustrate the utility of this procedure, iodophenyl derivatives were anchored on the same resin. A HRMAS-NMR analysis shed light on the reactivity of these heterocycles in Mitsunobu conditions. A subsequent diversification using a Sonogashira coupling produced a small array of novel (arylethynyl)-phenyl-1,2,4-oxadiazol-5-ones.
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1. Introduction

Various acidic heterocycles are classically used by medicinal chemists as carboxylic acid bioisosters.[1] Among these heterocycles, tetrazole is a key pharmacophoric group of the sartan family (antagonists of Angiotensin receptor).[2] It has also been incorporated into numerous biologically active series such as leukotriene antagonists, growth hormone secretagogues or metallo-β-lactamase inhibitors.[3] Other examples of acidic heterocycles are 1,2,4-oxadiazol-5-one, 1,2,4-oxadiazol-5-thione and 1,2,3,5-oxathiadiazol-2-oxide rings. In particular, 1,2,4-oxadiazol-5-one is found in AT1 antagonists, COX inhibitors, PLA2 inhibitors and modulators of GluR.[4] All these heterocycles can replace carboxylic acids but display geometrically different protomers and slightly different physico-chemical properties. Indeed, as shown in Table 1 on prototypal molecules, the pK_as of these heterocycles range between 3 and 5. Compounds bearing these heterocycles have different lipophilic properties that may translate into improved bioavailability compared with their tetrazole analogues.[4] In our project aiming at synthesizing various analogues of pharmacologically active carboxylic acids, that would display different pK_as and lipophilicity, we explored the use of solid supported reactions performed on polymer-linked heterocycles. In particular, we focused on 1,2,4-oxadiazol-5-one, 1,2,4-oxadiazol-5-thione and 1,2,3,5-oxathiadiazol-2-oxide. This strategy is inspired from solid phase peptide synthesis and retains from it the advantage of both the tractability of polymer supported chemistry and a single step for protection and anchoring of the acidic group. This strategy has been previously used for tetrazoles using a trityl chloride resin.[5] Here we describe and compare the use of two electrophilic resins: a trityl chloride resin and a HMPB-BHA resin (4-hydroxymethyl-3-methoxy-phenoxybutyric acid benzhydrylamine), the latter being used under Mitsunobu conditions. Anchoring on the HMPB-BHA resin was successfully applied to the synthesis of 3-(ethynyl-phenyl)-4*H*-[1,2,4]oxadiazol-5-one derivatives.

2. Preparation of prototypal heterocyclic compounds

Compounds **3**–**5** (Table 1) were synthesized using classical solution phase procedures.

Keywords: Acidic heterocycles; Solid phase; Mitsunobu reaction; Attachment; Cleavage; Sonogashira coupling.
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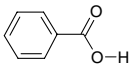
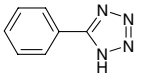
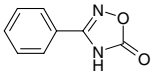
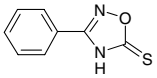
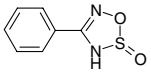
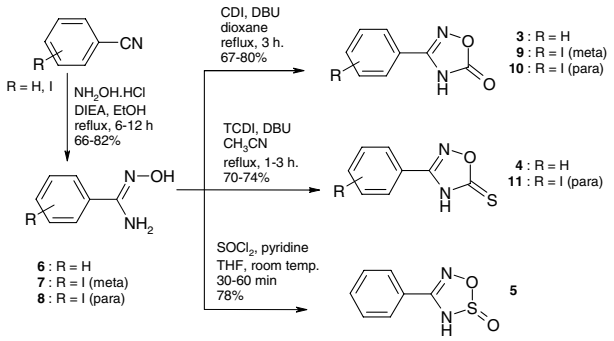
doi:10.1016/j.tetlet.2006.12.050

Table 1. Acidic heterocycles used as carboxylic acid bioisosters and their pK_a values

Compound			pK_a
	**1**	Benzoic acid	4.2[a]
	**2**	5-Phenyl-1*H*-tetrazole	4.5[b]
	**3**	3-Phenyl-4*H*-[1,2,4]oxadiazol-5-one	5.3[c]
	**4**	3-Phenyl-4*H*-[1,2,4]oxadiazol-5-thione	3.2[c]
	**5**	4-Phenyl-3*H*-[1,2,3,5]oxathiadiazole 2-oxide	4.8[c]

[a] From Ref. 18.
[b] From Ref. 19.
[c] pK_as were determined in H_2O–MeOH (1:1) by potentiometric titration using 0.025 M NaOH.



Scheme 1. Synthesis of prototypal heterocyclic compounds.

As described in Scheme 1, amidoximes **6**–**8** were prepared by the addition of hydroxylamine to the corresponding nitrile.[6] 1,2,4-oxadiazol-5-one **3** was obtained by treatment with 1,1′-carbonyldiimidazole (CDI) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[7] 1,2,4-oxadiazol-5-thione **4** was obtained via a similar route from **6** with 1,1′-thiocarbonyldiimidazole (TCDI) and DBU. 1,2,3,5-Oxathiadiazol-2-oxide **5** was prepared by the condensation of **6** with thionyl chloride in the presence of pyridine.[8]

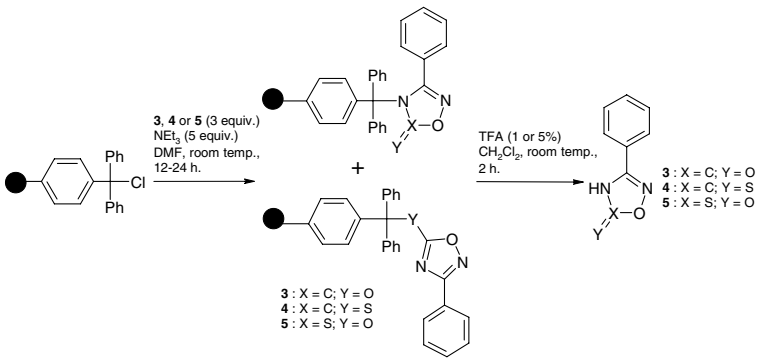
3. Development of a loading method with prototypal compounds 3–5 on a solid support

In the following section, we describe various anchoring schemes using trityl chloride or HMPB-BHA resins.

3.1. Method 1: loading on a trityl chloride resin

Reactions with the trityl chloride resin were performed using the alkylation conditions reported for the tetrazole ring.[5] (Scheme 2). In these conditions, only 3-phenyl 1,2,4-oxadiazole-5-thione (**4**) could be successfully anchored and recovered (Table 2). This result could be explained by the higher nucleophilicity of the sulfur-containing compound (**4**) compared to O- and N-nucleophiles in **3** and **4**.

Two attachment positions for heterocycles **3** and **4** may occur: via the N4 atom and via the exocyclic oxygen atom in **3** or via the exocyclic sulfur atom in **4**.



Scheme 2. Loading/cleavage of prototypal compounds **3**–**5** on trityl-chloride resin.

Table 2. Overall yields of loading/cleavage of prototypal compounds **3**–**5** on trityl-chloride resin

Compound	Cleavage: % TFA	Isolated yield (%)	Purity (%) (215 nM)
3	5	0	—
4	5	75	99
5	1[a]	0	—

[a] Compound **5** was unstable under 5% TFA conditions.

3.2. Method 2: loading on a HMPB-BHA resin

In a second attempt to anchor **3** and **5** on a solid support, we selected the HMPB-BHA resin, a primary benzylalcohol resin. In acidic media this resin generates a highly stabilized benzylic cation which is expected to ease the cleavage step.

Mitsunobu conditions have been reported for the solution phase alkylation of tetrazoles.[9] To our knowledge, only one report describes a solution phase alkylation of 1,2,4-oxadiazol-5-one with Mitsunobu conditions, although in poor yields.[10] In our experiments, triphenylphosphine (PPh_3) and diisopropyl-azodicarboxylate (DIAD) were used to anchor compounds **3**–**5** on the HMPB-BHA resin.

As reported in Table 3, these conditions proved to be efficient and allowed to recover the heterocycle in good yields and high purity. Interestingly, heterocycle **4** was loaded and recovered in a higher yield.

4. Application to the synthesis of acetylenic derivatives bearing the 1,2,4-oxadiazol-5-one ring

To demonstrate the usefulness of method 2 (iodophenyl) 1,2,4-oxadiazole-5-one **9** and **10** (Scheme 1) were loaded on a HMPB-BHA resin. Iodophenyl derivatives are versatile reagents that can be engaged in a variety of metallo-catalyzed reactions, under non-acidic conditions, to generate structural diversity through the formation of new CC bonds.[11]

Table 3. Overall yields of loading/cleavage of prototypal compounds **3**–**5** on HMPB-BHA resin

Compound	Cleavage: % TFA	Isolated yield (%)	Purity (%) (215 nM)
3	5	48	97
4	5	70	97
5	1[a]	45	96

[a] Compound **5** was unstable under 5% TFA conditions.

4.1. Loading of iodinated precursors and insight on their reactivity towards the alcohol function of the polymer under Mitsunobu conditions

Heterocycles **9** and **10** were loaded on the HMPB-BHA resin using the Mitsunobu conditions described in Scheme 3. Unreacted products were easily recycled. The loading was followed by HRMAS NMR (high resolution magic angle spinning NMR), a non-destructive technique that allows to monitor chemical reactions on a solid support.[12] ^1H HRMAS NMR spectrum of **10** bound to the resin showed that the loading was quantitative.[13] However, two distinct populations, corresponding to two attachment positions of the 1,2,4-oxadiazol-5-one heterocycle (O- or N4-alkylation) could be observed.[13,14] A HRMAS spectrum of the resin after acidic cleavage showed that only one population of **10** had been released. It was not possible to unambiguously identify which population (O- or N4-anchored) remained on the resin using solely HRMAS NMR. Compound **12** that closely mimics **10** when bound to the linker via N4 was prepared using solution phase chemistry (Fig. 1). Comparison of its NMR spectrum with the HRMAS spectrum of **10** bound to the resin showed that only the O-anchored population can be released from the resin.[15]

Conversely, a homogeneous population of 1,2,4-oxadiazol-5-thione **11** bound to the resin was observed by HRMAS. As expected, the heterocyclic ring is anchored via the exocyclic sulfur atom. This was confirmed by comparing the solution phase spectrum of **13** (Fig. 1) and the HRMAS spectrum of **11** bound to the resin.

All these observations are summarized in Scheme 4, and explain the moderate and very good yields obtained for 1,2,4-oxadiazol-5-one (**3**) and 1,2,4-oxadiazol-5-thione (**4**), respectively (Table 3).

4.2. Solid-phase Sonogashira coupling with polymer-supported 9 and 10

Supported compounds **9** and **10** were reacted with various alkynes via a Sonogashira coupling, as described in

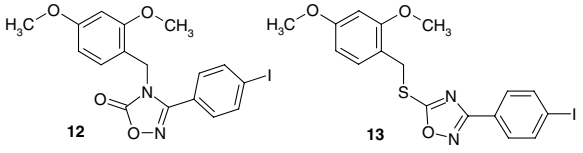
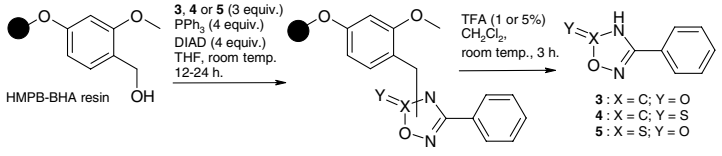
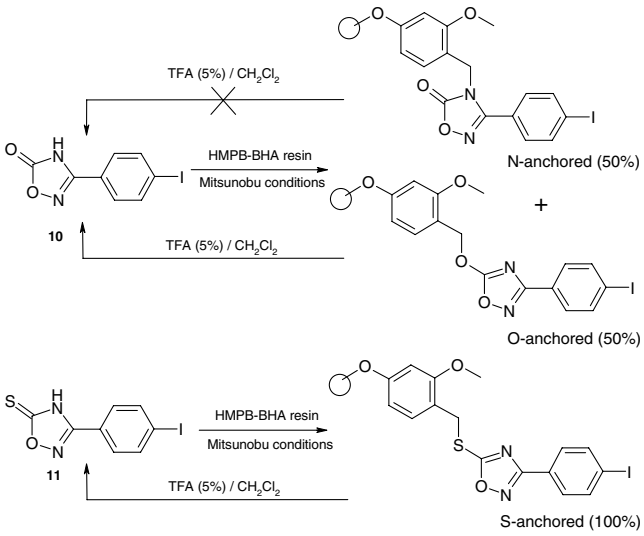


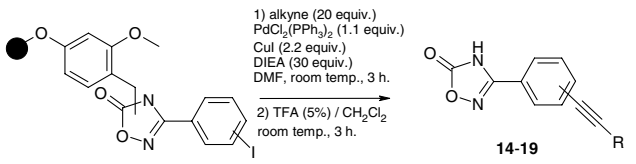
Figure 1. Structure of soluble analogues of polymer-bound **10** and **11** used for NMR assignments (detailed experimental procedure available in Supplementary data).



Scheme 3. Loading/cleavage of prototypal compounds **3**–**5** on HMPB-BHA resin.

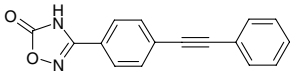
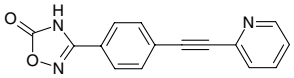
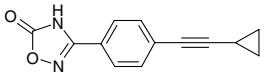
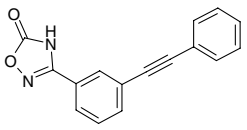
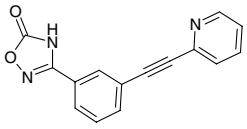
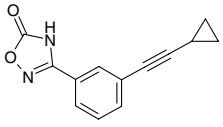


Scheme 4. Summary of the different anchoring modes of 1,2,4-oxadiazol-5-one or 1,2,4-oxadiazol-5-thione (evidenced by HRMAS NMR on para-iodo compounds **10** and **11**).



Scheme 5. Synthesis of compounds **14–19** via solid-phase Sonogashira coupling.

Table 4. Structures and yields of compounds **14–19**

	Compound	Isolated yield[a] (%)	Mp (°C)
14		35	247–249
15		30	216–218
16		32	230–231
17		35	182–185
18		37	152–154
19		35	187–188

[a] Purity >95% (LC, 215 nM).

Scheme 5.[16] Compounds **14–16** and **17–19** were obtained, respectively, from **9** and **10** after acidic cleavage and precipitation in a dichloromethane/petroleum ether mixture. Overall yields (three steps: loading, Sonogashira, cleavage) were satisfactory and purities were excellent (Table 4). No iodinated precursor (**9** or **10**) could be detected after cleavage showing that the Sonogashira coupling was quantitative.[17] No further purification was required.

5. Conclusion

We have shown that 1,2,4-oxadiazol-5-one and -thione, as well as 1,2,3,5-oxathiadiazol-2-oxide can be loaded on benzylalcohol resin using Mitsunobu conditions and retrieved from the polymer in good to excellent yields under mild acidic conditions. This anchoring has been shown to be compatible with solid-phase Sonogashira coupling conditions to produce a small array of (arylethynyl)phenyl-1,2,4-oxadiazol-5-ones. This method could find applications in medicinal chemistry, for the rapid polymer-supported synthesis of carboxylic acid surrogates.

Acknowledgements

We thank André Tartar for thoughtful comments and discussions. The authors would like to thank ARH Nord Pas de Calais for the financial support of NC. We are grateful to the institutions that support our laboratory (Inserm, Université de Lille2 and Institut Pasteur de Lille, Région Nord-Pas de Calais, EC).

Supplementary data

Full experimental details for **3–19**, as well as details for resins loading, ^{1}H HRMAS NMR data and solid-phase Sonogashira coupling. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.050.

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13. Same results were obtained for heterocycle **9**.
14. Mitsunobu conditions have been reported once to yield in solution phase a mixture of O- and N4-alkylated products. See Ref. 10. Only N4-alkylation is obtained using alkyl halides as electrophiles.
15. (a) Same results were obtained for heterocycle **9**; (b) Increasing percentage of TFA in DCM did not allow the release the N4-alkylated 1,2,4-oxadiazol-5-one heterocycle.
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17. Moderate yields reflect that only O-anchored product can be cleaved from solid support.
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