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Efficient one-pot preparation of 5-substituted-2-amino-1,3,4-oxadiazoles using resin-bound reagents

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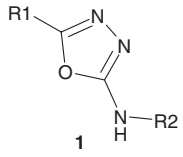
Abstract—A robust one-pot solution-phase synthesis of 2-amino-1,3,4-oxadiazoles directly from acylhydrazines and isothiocyanates is described. Commercially-available polymer-supported reagents help facilitate both cyclization and purification. This convenient method benefits from its broad applicability, ease and safety of reagent handling, simple product isolation, and the ability to perform multiple reactions in parallel fashion without need for purification. The details and scope of this reaction strategy are presented herein.

1. Introduction

Many 1,3,4-oxadiazoles are reported in the literature to have a broad spectrum of biological activity including antimicrobial,[1] antifungal,[2] anti-inflammatory,[3] and hypotensive activity.[4] During hit to lead efforts following a recent high throughput screening campaign, we initiated an SAR program that required the synthesis of a series of 5-substituted-2-amino-oxadiazoles **1**.



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Our objective was to prepare an array of 192 (12 R1 × 16 R2) 5-substituted-2-amino-oxadiazole analogues by rapid parallel synthesis. Literature syntheses of these oxadiazoles[5] include cyclodesulfurization of acylthiosemicarbazide derivatives in solution using I_2/NaOH or 1,3-dicyclohexylcarbodiimide (DCC),[6] as well as mercury(II) acetate ($Hg(OAc)_2$) or yellow mercury(II) oxide (HgO).[7] These latter methods require a full equivalent of Hg(II) and produce undesirable mercury byproducts that must then be removed and properly disposed of after the reaction is completed. Moreover, these methods are usually carried out in two discrete synthetic steps. In the first step, the reaction of the hydrazide **2** (Scheme 1) with an isothiocyanate (R2NCS) provides the acylthiosemicarbazide **3**, which is typically isolated from the reaction mixture and purified by recrystallization. In the second step, the cyclization is accomplished using one of the aforementioned conditions and the oxadiazole product **1** is frequently isolated and purified by recrystallization.

These solution-phase methods, while successful, were deemed not readily amenable to high throughput synthesis, and thus did not meet our needs. A solution-phase dehydrative synthesis from 1,2-diacylhydrazines[8] and several solid-phase methods were also considered.[9]

Here we report our efficient one-pot solution-phase preparation of 5-substituted-2-amino-1,3,4-oxadiazoles **1** directly from the acyl hydrazines **2** via commercially-available polymer-supported reagents. The key advantages of this method are the ability to perform multiple reactions with multiple substrates in parallel fashion, simplicity of work-up (simple filtration), ease and safety of reagent handling, and elimination of the need for purification as the products are typically obtained in high purity and good yields.

Keywords: Oxadiazole; 2-Amino-1,3,4-oxadiazole; 1,3,4-Oxadiazole; Carbodiimide; Acylhydrazine; Acylthiosemicarbazide; Parallel synthesis; Solid-supported reagents.
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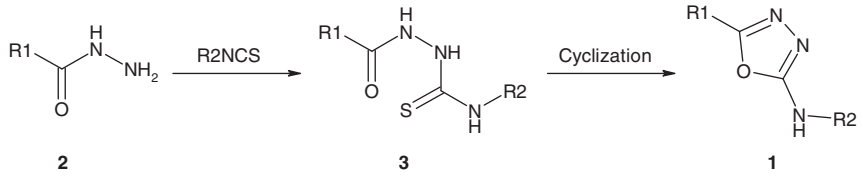


Scheme 1. Typical two-step solution-phase synthesis of oxadiazoles **1**.

2. Results and discussion

In order to prepare these compounds by rapid parallel synthesis, we needed a clean and efficient method to form the oxadiazoles, preferably directly from hydrazides **2** without isolation of **3**. Since multistep sequences can often be facilitated by use of resin-bound reagents,[10] and since the synthesis of 1,3,4-oxadiazoles via reaction of acylthiosemicarbazides **3** with DCC was known, it was logical to extend this method by using a resin-bound carbodiimide for the reaction with the additional advantage of a simplified work-up (Fig. 1).

The procedure described here was performed either in glass vials or fritted polypropylene or Teflon® reaction tubes.[11] Hydrazides **2a**–**h** were prepared by reaction of the corresponding ester with hydrazine[12] or purchased commercially (**2i**–**k**). Typically, 1.1 equiv of isothiocyanate were added neat to a solution of the hydrazide **2** (0.2 mmol) in 3 mL DMF. The resulting solution was allowed to mix at room temperature (rt) overnight (20 h). PS-Carbodiimide[13] (5 equiv) was added directly to the reaction solution with an additional 3 mL DMF to accommodate swelling of the resin. The vessels were then heated at 80 °C for 60 h. P-Propylamine (0.2 equiv) and PS-bemp (0.2 equiv) were added and the resin suspension was shaken an additional 17 h before collection of the desired product.[14] After collection of the filtrate and one wash of the resin (5 mL) with tetrahydrofuran (THF), final evaporation typically provided the oxadiazole **1** as a white solid in excellent purity[15] (as characterized by LCMS and ^{1}H NMR)[16] and good yield.[17] Representative results are shown in Table 1. Most of these products have not previously been reported in the literature. A typical ^{1}H NMR spectrum of isolated product is shown in Figure 2 for compound **1c**.

It is important to note that the one-pot conditions described herein (with cyclization temperature 80 °C, 60 h) represent a robust generic protocol that makes possible the synthesis of an array of 2-amino-1,3,4-oxadiazoles of diverse structure. However, we also determined that for many substrates, shorter reaction times, and milder cyclization conditions provide very comparable yields and purities. For example, cyclization

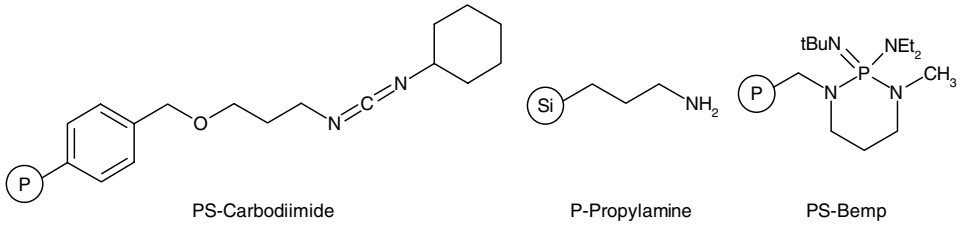


Figure 1. Structures of resin-bound reagents.

Table 1. Representative results using the described methods

Compound	R1	R2	% Yield[d]	LCMS purity[e]
1a[a]	2-F, 6-Cl-PhCH$_2$	Ph	74	90
1b[a]	3,4-Di-Cl–PhCH$_2$	Ph	75	96
1c[a]	3-Pyridyl–CH$_2$	Ph	82	100
1d[a]	3,4-OCH$_2$OPhCH$_2$	Ph	73	86
1e[b]	2-F, 6-Cl-PhCH$_2$	Isobutyl	69	100
1f[b]	3,4-Di-Cl–PhCH$_2$	Isobutyl	72	100
1g[b]	3-Pyridyl–CH$_2$	Isobutyl	64	100
1h[b]	3,4-OCH$_2$OPhCH$_2$	Isobutyl	73	100
1i	Ph	Me	71	100
1j	Ph	Isobutyl	76	91
1k[c]	Ph	Ph	67	96

[a] Alternative method A: Step 2, rt, 20 h.
[b] Alternative method B: Step 2, 80 °C, 20 h.
[c] Alternative method C: Step 2, rt, 40 h.
[d] Isolated product yield.
[e] Identity and purity determined by LCMS using UV 214 detection.

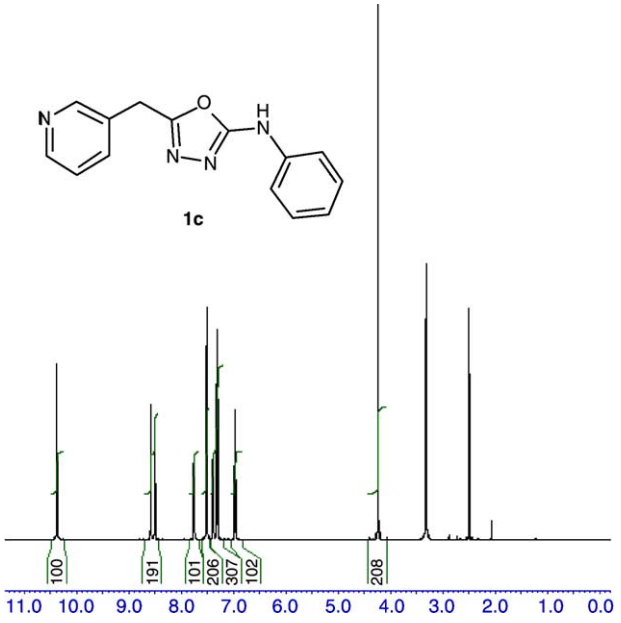
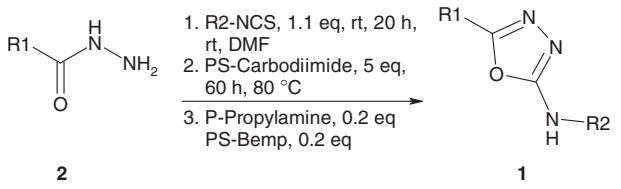


Figure 2. ^{1}H NMR (400 MHz, DMSO-d_6) of representative oxadiazole **1c**.



Scheme 2. Improved one-pot solution-phase preparation of 2-amino-oxadiazoles **1**.

to the oxadiazole is accomplished at room temperature for analogues derived from aryl isothiocyanates (i.e., **1a**–**d**,**k**). These alternative conditions are provided in the footnotes of Table 1.

This simple one-pot method (Scheme 2) can be applied using simple glass or plastic reaction vials on a variety of parallel synthetic platforms including the Robbins Flex–Chem™ system, Mettler–Toledo Bohdan MiniBlocks™, and the Argonaut Quest™ 210. In this case, the SAR array of approximately 200 oxadiazoles was successfully prepared using polypropylene reaction tubes in conjunction with the MiniBlock™ synthesis system.

3. Conclusion

In summary, we report a robust one-pot solution-phase synthesis of 2-amino-1,3,4-oxadiazoles directly from acylhydrazines and isothiocyanates. Commercially-available polymer-supported reagents help facilitate both cyclization and purification. To our knowledge, an efficient one-pot solution-phase preparation of 5-substituted-2-amino-1,3,4-oxadiazoles **1** directly from the acylhydrazines **2** via commercially-available polymer-supported reagents has not been reported, though the use of solid-supported reagents and scavengers in multistep syntheses is well known. This convenient and useful method benefits from its broad applicability, ease and safety of reagent handling, simple product isolation, and the ability to perform multiple reactions in parallel fashion without need for purification.

Acknowledgements

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11. Reagents were obtained from either the Aldrich Chemical Co., Lancaster Synthesis, or Alfa/Aesar Organics and used without further purification.
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13. PS-Carbodiimide (Cat. no 800371, 1.1 mmol/g) was obtained from Argonaut Technologies, 1101 Chess Drive, Foster City, CA 94404.
14. 3-Aminopropyl functionalized silica gel (Aldrich, 1.0 mmol/g) was added to scavenge the excess isothiocyanate from the first step. PS-Bemp (Fluka, Cat. no 20026, 2.2 mmol/g) was added to scavenge any unreacted acylthiosemicarbazide, though this was typically not observed by LCMS.
15. Purity data reported here was determined by a C18 reverse phase HPLC column [Keystone Aquasil (1×40 mm)] in 10–90% ACN/H_2O containing 0.02% TFA (3.6 min gradient) and monitored by a UV detector operating at 214 nm and by a SEDEX 75 evaporative light scattering detector (ELSD) operating at 42 °C. LCMS [M+H] signals were consistent with expected MW for all reported products.
16. Physical data for **1c**: ^{1}H NMR (d_6-DMSO, 400 MHz): δ 10.38 (1H, s, NH), 8.59 (1H, d, $J = 2.0$ Hz), 8.51 (1H, dd, $J = 4.8$, 1.6 Hz), 7.76 (1H, dt, $J = 8.0$, 2.0 Hz), 7.52 (2H, dt, $J = 8.0$, 2.0 Hz), 7.40 (1H, ddd, $J = 8.0$, 4.8, 0.8 Hz), 7.32 (2H, ddd, $J = 8.0$, 2.0, 0.8 Hz), 6.97 (1H, app dt, $J = 7.2$, 0.8 Hz), 4.24 (2H, s). LCMS [M + H] = 253.2, 1.28 in., 100% purity (UV 214 nm).
17. All compounds reported herein were characterized by ^{1}H NMR to confirm the purity assessment of the LCMS data.