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An Improved Synthesis of 1,2,4-Oxadiazoles on Solid Support

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Abstract—The use of tetra-*N*-butylammonium fluoride (TBAF) as a mild and efficient reagent for the cyclodehydration of *O*-acyl amidoximes has been extended to the synthesis of 1,2,4-oxadiazoles on solid support. Argopore MB-CHO resin (Argonaut Technologies) was reductively aminated and subsequently acylated with 4-cyanobenzoyl chloride. Conversion of the nitrile to the amidoxime and acylation with a range of acid chlorides in parallel followed by treatment with TBAF under ambient conditions afforded a library of 3,5-disubstituted 1,2,4-oxadiazoles.

3,5-Functionalized 1,2,4-oxadiazoles have received considerable attention in the pharmaceutical industry as heterocyclic amide and ester isosteres.[1] Furthermore, oxadiazoles have been employed in the design of numerous biologically active templates. Examples include muscarinic agonists,[2] tyrosine kinase inhibitors,[3] antiinflammatory agents,[4] histamine H3 antagonists,[5] antitumor agents,[6] and monoamine oxidase inhibitors.[7] Our desire to incorporate this useful template into diverse combinatorial screening libraries has led to the examination of tetra-*N*-butylammonium fluoride (TBAF) induced *O*-acylamidoxime cyclodehydration on solid support. The use of TBAF as an efficient and catalytic reagent for the synthesis of 3,5-disubstituted 1,2,4-oxadizoles from *O*-acylamidoximes has been recently reported.[8] Alternative approaches to the synthesis of oxadiazoles on solid support have been reported independently and typically rely on the thermal cyclodehydration of *O*-acylamidoximes at elevated temperatures.[9,10] In one report, the use of excess sodium ethoxide in ethanol afforded the desired oxadiazole at ambient temperature, but only on extended reaction times.[11] Herein we report that the use of TBAF readily and efficiently affords 3,5-disubstituted oxadiazoles on solid support at room temperature.

The general synthetic strategy employed in our study is illustrated in Scheme 1. Argopore MB-CHO resin (Argonaut Technologies, 0.9 mmol g^{-1}) was reductively aminated by treatment with an excess of benzylamine in trimethylorthoformate, followed by imine reduction using sodium cyanoborohydride.[12] Benzylamine acylation was carried out by reacting the amine resin with a DMF solution of 4-cyanobenzoyl chloride in the presence of pyridine and catalytic DMAP. The resin bound nitrile thus obtained was then efficiently converted to the amidoxime by treatment with an excess of 50% aqueous hydroxylamine in refluxing ethanol over 1 h. Acylation of the amidoxime was then carried out with 25 commercially available acid chlorides in parallel using a Bohdan MiniBlock™ reactor and Tecan™ liquid handler. The amidoxime bound resin was suspened in DMF and treated with the selected acid chlorides (5.6 equiv) in the presence of excess pyridine for 30 min. Each of the acid chlorides purchased was employed directly without further purification. Cyclodehydration was then effected by treatment with TBAF (2.2 equiv) in THF over 12 h under ambient conditions. The use of a 2-fold excess of TBAF appears to be necessary to achieve complete conversion to the oxadiazole. (In the case of acetyl substrate **4a**, the use of stoichiometric TBAF afforded only partial cyclodehydration to **5a** even on extended reaction times.) Cleavage of the desired oxadiazoles from resin was carried out using 95% aq TFA and the products isolated were analyzed by LCMS after drying.

The results of this preliminary survey are summarized in Table 1. (With very limited exception the oxadiazole products were directly isolated in 70% or greater purity based on analytical HPLC with no major side reactions apparent.) The methodology appears to be quite general

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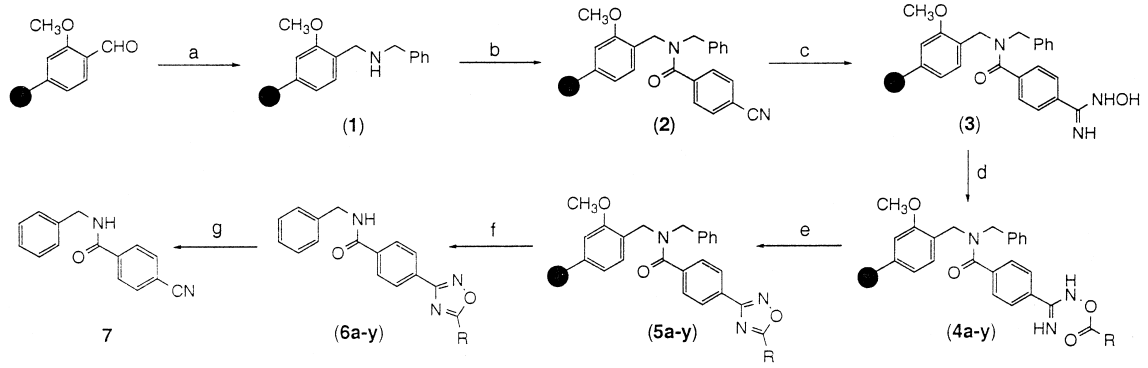
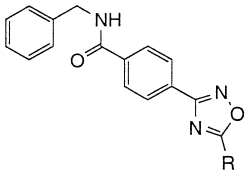


Scheme 1. Oxadiazole synthesis strategy. Reagents and conditions: (a) $(MeO)_3CH$, $PhCH_2NH_2$; $NaBH_3CN$, HOAc, THF; (b) 4-cyanobenzoyl chloride, DMAP, DMF, pyridine; (c) 50% aq NH_2OH, EtOH, reflux; (d) RCOCl, pyridine, DMF; (e) TBAF, THF; (f) 95% TFA; (g) for **6g** only, TBAF, THF.

Table 1. Results for oxadiazole **6** formation



Substrate	R	% Yield[a]	HPLC purity[b]	Mass detected[c]
6a	Methyl	29	95	316.1
6b	Cyclopropyl	38	80	342.2
6c	Cyclobutyl	27	95	356.1
6d	Cyclopentyl	19	92	370.1
6e	Cyclohexyl	38	100	384.2
6f	*tert*-Butyl	48	92	336.1
6g	Phenyl	25	86	378.1
6h	Phenylacetyl	29	15	368.1
6i	Hydrocinnamyl	17	90	406.2
6j	2-Methoxyphenyl	21	77	408.1
6k	3-Methoxyphenyl	27	87	408.1
6l	4-Methoxyphenyl	17	66	408.1
6m	2-Fluorophenyl	40	74	396.1
6n	3-Fluorophenyl	26	79	396.1
6o	4-Fluorophenyl	30	88	396.1
6p	Mesityl	47	63	420.2
6q	4-Biphenyl	15	68	454.1
6r	1-Naphthyl	18	79	428.1
6s	2-Naphthyl	26	87	428.2
6t	2-Furyl	38	55	368.1
6u	Thiophene-2-yl	52	77	384.1
6v	4-Pyridyl	44	91	379.1
6w	3-Pyridyl	22	78	379.1
6x	3,5-Dimethyloxazol-2-yl	34	100	379.1
6y	1-Phenyl-5-propylpyrazol-4-yl	21	88	464.2

[a]Percent yield based on theoretical resin loading of 0.9 mmol/g.
[b]Analytical HPLC was performed using a YMC-ODS 3×50 mm reverse phase column using a 2 min 10–90% methanol gradient in 0.1% TFA buffered water eluent with absorbance detection at 254 nm.
[c]LRMS (EI) values reported are either M^+ or MNa^+.

with respect to substitution at the oxadiazole 5-position, with a range of aliphatic, aromatic and heterocyclic substituents being well tolerated. A surprising exception was noted in the case of phenylacetyl substrate **4h**. (In this case, the oxadiazole **6h** was detected as a minor component (15% by HPLC) with the major product being the corresponding nitrile **7**.) (Although the preparation of **6h** in solution phase using TBAF in THF (1.0 equiv, 5 min) affords the oxadiazole in 72% isolated yield, the subsequent treatment of **6h** in THF solution with TBAF (2.2 equiv, 12 h) efficiently gives nitrile **7**. Presumably, oxidation to the 5-benzoyl derivative **6** (R = C(O)Ph) followed by hydroxide mediated fragmentation of the resulting ketone affords oxadiazole **6** (R = H) and benzoic acid. Subsequent base promoted oxadiazole fragmentation may then afford the nitrile.[13] The observation of a transient species by LCMS (M + 14) and the detection of benzoic acid in the reaction mixture provide support for this mechanistic hypothesis.) An additional limitation was observed in the case of 2,4,6-trimethylbenzoate **4p**. For this substrate, LCMS analysis after resin cleavage revealed that ring closure remained incomplete under the reaction conditions employed, affording a 3:1 ratio of 5-mesityloxadiazole **6p** and the corresponding *O*-acylamidoxime. The relatively slow rate of ring closure may be due to a steric effect associated with the aromatic ring 2,6-substituents.

In summary, we have delineated some key aspects of the generality of TBAF mediated cyclodehydration of *O*-acylamidoximes to oxadiazoles on solid support. With very limited exception, the methodology appears to have a broad scope with respect to variation at the oxadiazole 5-position. The relatively mild reaction conditions employed suggests that the construction of highly diverse combinatorial libraries comprised of 3,5-disubstituted 1,2,4-oxadiazoles is practical. Studies aimed at the further development of this methodology and its application to the production of combinatorial high-throughput screening libraries is in progress.

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