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An efficient solid-phase of 3-alkylamino-1,2,4-oxadiazoles

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Abstract—A solid-phase synthesis of substituted 3-alkylamino-1,2,4-oxadiazoles has been developed. The synthesis utilizes immobilized *N*-acyl-1*H*-benzotriazole-1-carboximidamides as key intermediates. Cyclization with hydroxylamine under mild conditions furnished the oxadiazole skeleton regioselectively in high yield and purity.

Oxadiazoles, heterocyclic isosteres of metabolically labile amide and ester functionalities have been evaluated in numerous therapeutic areas such as antivirals,[1] muscarinic receptor antagonists,[2] benzodiazepin receptor antagonists,[3] histamin H3-receptor antagonsists,[4] acetylcholinesterase inhibitors,[5] and dual 5-lipoxygenase and cyclooxygenase inhibitors.[6] 3-Alkylamino-1,2,4-oxadiazoles have been prepared in solution phase by a photochemical rearrangement starting from 3-amino-1,2,5-oxadiazoles (furazans),[7] and condensation of cyanoamines or isothioureas with hydrazines.[8] The most common route to 1,2,4-oxadiazoles, the condensation of amide oximes with acylating agents,[9] has successfully been transferred to solid support using anhydrides[10] and esters[11] as electrophiles.

Recently, we reported a solid-phase synthesis of aminotriazoles using *N*-acyl-1*H*-benzotriazole-1-carboximidamides as key intermediates.[12] These electrophiles (**3**) are solid-phase equivalents of a similar species first reported by Katritzky et al. for the synthesis of aminotriazoles[13] and aminotriazinones.[14] It was anticipated that resin-bound *N*-acyl-1*H*-benzotriazole-1-carboximidamides can also serve as intermediates in the high-throughput synthesis of aminooxadiazoles.

Intermediate **3a** was prepared according to the published method[12] and was subjected to cyclization with hydroxylamine. Initially, hydroxylamine hydrochloride was free-based with the aid of excess DIPEA, but no desired product was obtained upon cleavage with TFA. On the other hand, slight excess of DBU mixed with hydroxylamine hydrochloride and resin **3a** gave rise to the expected product **5a**. An extensive wash protocol (THF, H_2O, 1% AcOH/H_2O, THF, IPA, toluene, IPA, DCM) was required to completely remove DBU hydrochloride before cleavage with TFA. Although THF was typically the solvent of choice in the cyclocondensation step, dimethylacetamide proved to be equally effective (**5b**, Table 1). A potential side reaction, route B reported in the solution phase synthesis of aminotriazoles, did not pose difficulties using our optimized method. 4-Hydroxy-2-methoxybenzyl derivatives (**7**), the typical cleavage products[15] of resin bound R_1 amines when reaction route B (Scheme 1) takes place, were detected during method development for aminotriazoles.[12] No trace of **7a**–**n** was detected for entries in Table 1.

The results of our solid-phase method applied to a diverse set of alkyl and aryl substituents at both sites are depicted in Table 1. Both alkyl and aralkyl amines are well tolerated at R_1, but anilines (**5o**) are not compatible with the current method. Sterically hindered amines at R_1 may require forcing conditions or repeated couplings to effect full conversion to 1*H*-benzotriazole-1-carboximidamides (**2**). As an example, **5d** was contaminated by 30% amide **9**. At R_2, in general, both alkyl and aryl acid chlorides gave crude aminooxadiazoles in good purity (Table 1). Inductive effects (**5j**,**k**) do not significantly influence the outcome of the cyclocondensation with hydroxylamine. Methyl oxalyl chloride yielded an unidentified mixture of products (**5n**). Aminooxadiazoles of sterically hindered (**5l**) acid chlorides were obtained with lower purity due to partial conversion during the acylation step. All com-

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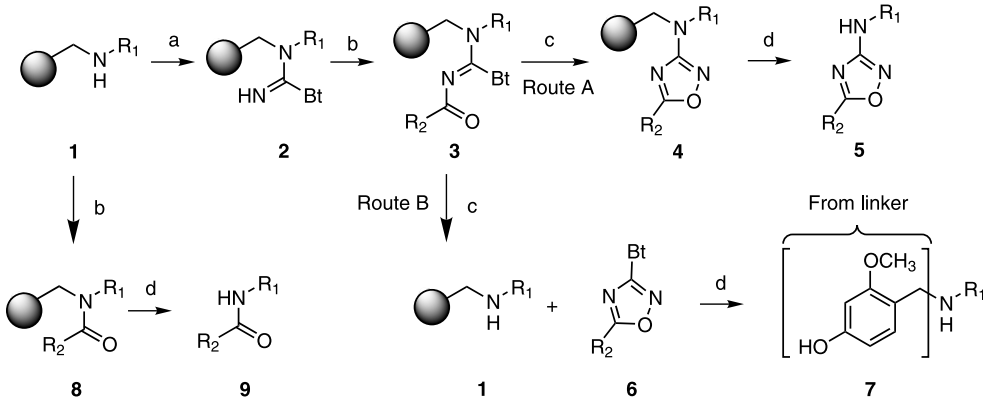
Table 1. Crude 3-alkylamino-1,2,4-oxadiazoles (**5**) synthesized according to the procedure in Scheme 1

	R_1	R_2	Purity[a]	m/z	Yield[b]
a	4-Methylbenzyl	4-Methylphenyl	95	280	85
b	4-Methylbenzyl	4-Methylphenyl	95[c]	280	85
c	3-Pentyl	4-Methylphenyl	90	246	80
d	1-Benzyl-2-methoxyethyl	4-Methylphenyl	65	324	80
e	Cyclohexanemethyl	4-Methylphenyl	95	272	85
f	Phenylpropyl	4-Methylphenyl	95	294	90
g	3-Methoxypropyl	4-Methylphenyl	95	248	95
h	4-Methylbenzyl	*t*-Butyl	90[d]	246	80
i	Isobutyl	Cyclohexyl	95	224	80
j	Isobutyl	4-Methoxyphenyl	90[d]	248	75
k	4-Methylbenzyl	2,4-Difluorophenyl	90[d]	302	75
l	4-Methylbenzyl	2,6-Dimethoxyphenyl	25	326	75
m	4-Methylbenzyl	4-Chlorobenzyl[c,e]	95	266	85
n	Isobutyl	Methyl oxalyl	10	200	85
o	4-Methoxyphenyl	4-Methylphenyl	N/A	N/A	0

[a] % by ELSD–HPLC of the desired ion.
[b] 10% bead loss for each resin transfer is typical and is included.
[c] Reaction was carried out in DMA as a solvent for step c (Scheme 1).
[d] Contaminant: DBU hydrochloride.
[e] 2,6-Di-*t*-butyl-4-methylpyridine was used as a base for step b (Scheme 1).

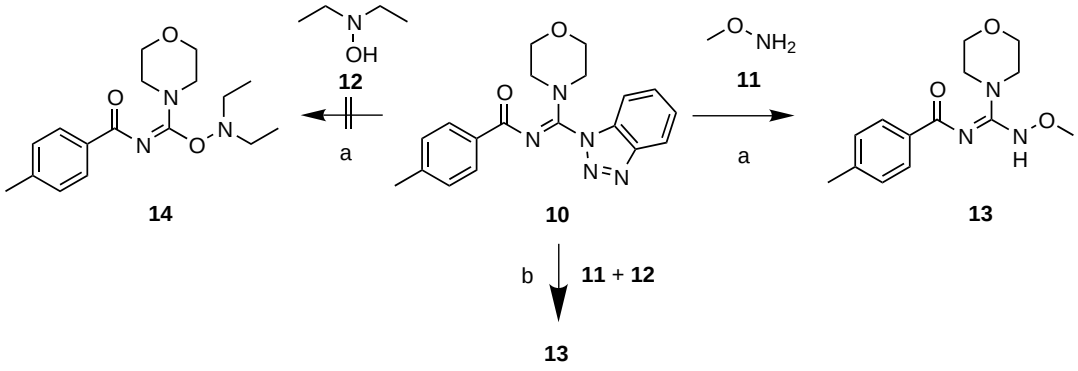


Scheme 1. Synthesis of 3-alkylamino-1,2,4-oxadiazoles. *Reagents and conditions*: (a) 3 equiv. $Bt_1C(=NH)Bt_1$+$Bt_1C(=NH)Bt_2$/THF/rt/argon; (b) 5 equiv. R_2COCl/10 equiv. DIPEA/DCM/rt; (c) 10 equiv. H_2NOH HCl/12 equiv. DBU/THF or DMA/50°C; (d) TFA/DCM = 95:5.

pounds were characterized by HPLC, LC–MS and ^1H NMR.[16]

Aminooxadiazoles were furnished with high regioselectivity as confirmed by ^1H NMR and a single peak by two different HPLC methods. The reaction of hydroxylamine with resin **3** can theoretically generate two isomers. Initial attack on the sp^2 carbon by the hydroxylamine nitrogen gives rise to 3-alkylamino1,2,4-oxadiazoles, while that by the hydroxylamine oxygen yields 5-alkylamino-1,2,4-oxadiazoles. In order to substantiate the identity of the obtained oxadiazole isomers, model[14] compound **10** was synthesized in solution and reacted with monofunctional hydroxylamine derivatives **11** and **12**, respectively (Scheme 2). The reaction mixtures were analyzed by LC-MS to find that **11** readily displaced the benzotriazole, but no reaction was observed with **12** (only hydrolyzed **10** was detected). In addition, **10** in the presence of an equimolar mixture of **11** and **12** produced a single product, **13**. ^1H NMR spectra of **5e** synthesized by the method herein and via alternative literature methods[17] were found to be identical. Thus, it can be concluded that our solid-phase protocol produces 3-alkylamino-1,2,4-oxadiazole isomers.

In summary, a facile synthesis of 3-amino-1,2,4-oxadiazoles with two diversity points has been developed. The method involves cyclocondensation of hydroxylamine with *N*-acyl-1*H*-benzotriazole-1-carboximidamides. Our methodology enables the synthesis of 3-amino-1,2,4-oxadiazole combinatorial libraries in parallel or with the split-and-pool technique.



Scheme 2. Identification of aminooxadiazole isomers. *Reagents and conditions*: (a) 1.1 equiv. **11** or **12**/1.2 equiv. DBU/THF/50°C; (b) 1.1 equiv. **11**/1.1 equiv. **12**/2.5 equiv. DBU/THF/50°C.

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15. Typically observed for products containing an ionizable amine at the benzylic linker attachment using 4-formyl-3-methoxyphenoxymethyl polystyrene resins.
16. ^{1}H NMR spectra for representative compounds: **5e**: 400 MHz, acetone-d_6 δ 7.92 (d, 2H), 7.38 (d, 2H), 3.13 (t, 2H), 2.42 (s, 3H), 1.83 (d, 2H), 1.80–1.60 (m, 4H), 1.36–1.20 (m, 3H), 1.10–0.95 (m, 2H). **5m**: 400 MHz, acetone-d_6 δ 7.39 (s, 4H), 7.24 (d, 2H), 7.13 (d, 2H), 4.35 (t, 2H), 4.15 (s, 2H), 2.29 (s, 3H).
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