ORGANIC LETTERS

2002
Vol. 4, No. 10
1751−1754

# Solid-Phase Synthesis of 3-Alkylamino-1,2,4-triazoles

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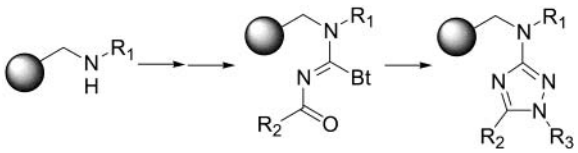
**Received March 5, 2002**

## ABSTRACT




**A solid-phase synthesis of trisubstituted 3-alkylamino-1,2,4-triazoles has been developed. The synthesis utilizes immobilized *N*-acyl-1*H*-benzotriazole-1-carboximidamides as key intermediates. Cyclization with hydrazines under mild conditions furnishes the title compounds with regioselectivity and high purity.**

The aminotriazole system has been known to be an important recognition element in biologically active molecules. Inhibitors of catalase[1] and histidine biosynthesis[2] include 3-aminotriazole derivatives. 3-Aminotriazoles have been found effective for the treatment of chronic bronchial asthma[3] and have been assessed as herbicides.[4] Sufotidine bismuth citrate, an aminotriazole histamine $H_2$-receptor antagonist, is used to treat histamine-mediated conditions such as ulcers.[5] 3-Aminotriazoles have also been patented as neuropeptide Y receptor ligands.[6]

Synthesis of 1,2,4-triazoles on the solid phase has been reported using two strategies. In the first method, dehydration of amidrazones was shown to yield 1,2,4-triazoles.[7] The scaffold was attached to the resin via the $N_1$ triazole nitrogen preventing the production of $N_1$-substituted analogues using this strategy. At the same time, the number of diversity points was limited to two, at positions 3 and 5. In an alternative methodology, a resin-bound acyl hydrazine, when reacted with amidines was converted to 3,5-disubstituted-1,2,4-triazoles.[8] Alkylation of this intermediate with alkyl bromides gave an uncontrolled mixture of *N*-alkyl triazole regioisomers. As a result of the need for resin linkage through a phenolic oxygen, full diversity at one of the substitution sites at position 3 or 5 cannot be achieved using this approach either.

Numerous methods have been developed for the solution-phase synthesis of 3-amino-1,2,4-triazoles. These include the reaction of aminoguanidines with carboxylic acids[9] and cyclization of hydrazones made from aminoguanidines[10] or amidrazones with carbodiimides.[11] Moreover, 3-alkylamino analogues have been prepared from preformed 3-amino-triazoles by reductive alkylation.[12]

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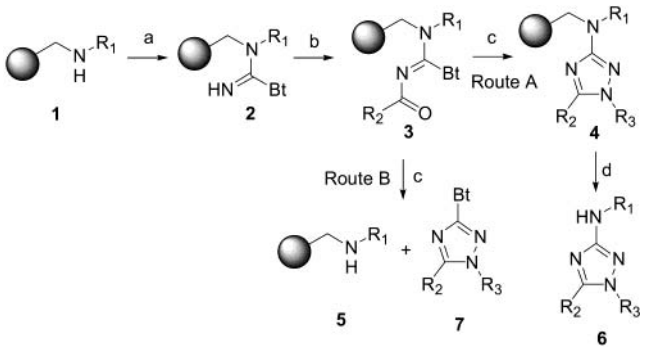
10.1021/ol025821i CCC: $22.00 
**Published on Web 04/12/2002**

Katritzky et al. have recently reported the solution-phase synthesis of *N*,*N*-disubstituted 3-amino-1,2,4-triazoles.[13] The key intermediates, acylated benzotriazole-1-carboximidamides, were prepared in two steps and were reacted with hydrazines to form the triazole ring system. Attractive features of this method include (a) the final products are obtained regioselectively and (b) all synthetic steps are carried out under mild conditions. However, only methylhydrazine led to clean conversion to the desired aminotriazoles; products derived from other hydrazines were contaminated with substantial amounts of 3-benzotriazole-substituted 1,2,4-triazoles (Scheme 1, route B). Moreover, all intermediates and products required purification by chromatography.

**Scheme 1**[a,17]




[a] (a) 3 equiv of $Bt^1C(=NH)Bt^1$+$Bt^1C(=NH)Bt^2$/THF/rt/argon; (b) 5 equiv of $R_2COCl$/10 equiv of DIEA/DCM/rt; (c) 5 equiv (10 equiv for $R_3$=Me) of $R_3NHNH_2$/12 equiv of DBU/THF/50 °C/argon; (d) TFA/DCM (95:5).

We reasoned that a synthetic sequence similar to Katritzky's approach, if successfully applied to the solid-phase technique, could deliver significant benefits. Regioselectivity observed in solution phase would likely be retained as a result of an analogous mechanism starting with the attack of the primary amine of the hydrazine on the resin-bound benzotriazole activated $sp^2$ carbon (Scheme 1). The 3-benzotriazole-substituted 1,2,4-triazole byproducts (**7**), if formed during synthesis, would be released prematurely from the resin and washed away. The residual resin-bound amines (**5**) are cleaved very slowly using the acid-sensitive formyl linkers. Thus, the desired 3-alkylamino-1,2,4-triazoles (**6**) were expected with higher purity than in solution. Ease of adaptation to parallel synthesis and the potential use of intermediate **3** for the synthesis of other amino heterocycles make the solid-phase approach even more attractive. Consistent with this expectation, a solution-phase route to amino-1,3,5-triazinones starting from intermediates similar to **3** has been reported.[14]

To our knowledge, no solid-phase synthesis of *N*-acyl-1*H*-benzotriazole-1-carboximidamide species has been communicated to date. Although benzotriazole-1-carboximidamides (the solution-phase equivalent of **2**) have been prepared with no displacement of the second benzotriazole by the amine reactant at room temperature, such substitutions take place readily at elevated temperatures.[15]

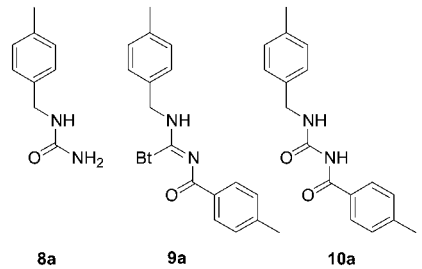
The use of site-isolated *resin-bound* secondary amines, generated by the standard solid-phase protocol ($NaBH(OAc)_3$/1%AcOH/DMF),[16] in the preparation of **2** prevents further reactions with the second benzotriazole. It was unknown whether intermediate **2** is hydrolytically stable enough to withstand exposure to air during a standard solid-phase wash protocol.

For evaluation, we synthesized **3a** (substituents are as shown in Table 1 for triazoles **6**) and cleaved it from the solid support. The di(benzotriazolyl)methanimine reagent (a mixture of bis-$N_1$- and mixed $N_1$,$N_2$-substituted isomers, where only the $N_1$-subtituted benzotriazole is reactive) was synthesized in one step by the literature method.[15] If hydrolysis of intermediate **2** occurred then urea byproduct **8a** would be observed along with the expected **9a** and **10a** upon cleavage of intermediate **3a** with TFA. Urea **8a** would be present because acylation of ureas does not take place under the mild acylating conditions, while **9a** was anticipated to be prone to hydrolysis under the acidic cleavage conditions giving rise to **10a**.

**Table 1.** Crude 3-Alkylamino-1,2,4-triazoles (6) Synthesized According to the Procedure in Scheme 1

| | $R_1$ | $R_2$ | $R_3$ | purity[a] | yield[b] |
|---|---|---|---|---|---|
| **a** | 4-MeBn | 4-MePh | Me | 95 | 65 |
| **c** | 4-MeBn | 4-MePh | Bn | 95 | 45 |
| **d** | 4-MeBn | 4-MePh | 4-MeOPh | 95 | 45 |
| **e** | *s*-butyl | *c*-hexyl | Me | 95 | 65 |
| **f** | *s*-butyl | *c*-hexyl | Bn | 95 | 45 |
| **g** | *s*-butyl | *c*-hexyl | 4-MeOPh | 95 | 45 |
| **h** | 4-MeOPh | 4-MePh | Me | n/a | 0 |

[a] By ELSD-HPLC of the desired ion. [b] Isolated yields; 10% bead loss for each resin transfer is typical at the 25 $\mu$mol scale and is not included, estimated yields of the overall chemical transformations are about 150% of yields isolated as a result of 4 resin transfers.




When resin **2** was filtered, washed with THF and dichloromethane (3× each), and immediately subjected to acylation,

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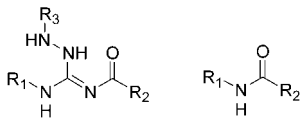
no trace of **8a** was found when resin **3a** was cleaved with TFA. The ratio of **10a** and **9a**, conveniently monitored by LC-MS, varied depending on exact cleavage conditions, but **10** was found to be the dominating species in all cases when intermediates **3a**−**h** were analyzed.



**11**



**12**

Our initial test reaction with hydrazine (without the use of additional base) showed the presence of a significant amount of uncyclized intermediate **11b** ($R_1$ = 4-MeBn, $R_2$ = 4-MePh, $R_3$ = H) besides **6b** after TFA treatment. This observation is in contrast with the outcome of the solution-phase procedure, which gave optimal results at room temperature. However, full conversion of **3a** to **4a** (using methylhydrazine) was achieved at either room temperature or 50 °C with no appreciable formation of intermediate **11a**. No product was detected using phenylhydrazine at either room temperature or 50 °C. Importantly, when excess base was added to the reaction mixture, the desired product was formed with varying purity. The use of DIPEA gave rise to a large number of byproducts besides the expected triazole, and potassium *tert*-butoxide (solution in THF) furnished the triazole irreproducibly. Species **10**, which can arise from either hydrolysis of **3** or alkylation of the butoxide anion with concomitant TFA deprotection of the resultant imidate, was always present in significant amounts. The apparent yields with DIPEA and KO*t*Bu were always low probably because of formation and premature release of the 3-benzotriazole substituted 1,2,4-triazoles as observed by Katritzky in solution.[13]

Gratifyingly, DBU proved to be superior to all other bases and furnished the desired products in high purity with good yields. To establish the extent of benzotriazole-substituted triazole (**7d**, route B) formation, **4d** (prepared with the optimized procedure) was subjected to acylation with 4-methoxybenzoyl chloride. Approximately 30% of the amide formed by the resin-bound amine $R_1$ (**5**) with *p*-methoxybenzoyl chloride was detected. Since **3d** is made with an analogous acylating protocol utilizing *p*-toluoyl chloride in the previous step, the presence of the *p*-methoxybenzamide derivative must be due to the reaction route leading to **7**. The 70/30 partition is significantly better than previously observed, and thus the use of DBU in the corresponding solution-phase reactions[13] is expected to improve purities and yields for 3-aminotriazoles.

(17) StratoSpheres PL-FMP (4-formyl-3-methoxyphenoxymethyl) resin was used for all solid-phase procedures. Intermediate **3** was prepared as follows. Resin **1** (0.025 mmol) and $Bt^1C(=NH)Bt^1$+$Bt^1C(=NH)Bt^2$ (20 mg, 0.075 mmol) in THF (1 mL) was flushed with argon and tumbled overnight at room temperature. The resin was filtered and washed with THF (3×) and dichloromethane (3×) to give resin **2**. To resin **2** (0.025 mmol) was added dichloromethane (1 mL), DIPEA (44 μL, 0.25 mmol), and $R_2COCl$ (0.125 mmol). The mixture was tumbled overnight at room temperature. The resin was filtered and washed with dichloromethane (3×), 2-propanol (3×), and dichloromethane (3×) to give resin **3**.

The results of this solid-phase procedure applied to a sparse matrix of alkyl and aryl substituents at all three sites are shown in Table 1. Anilines at $R_1$ apparently did not generate intermediate **2** at room temperature, because only **12h** could be recovered. Only a trace of intermediate **3h** was observed when the reaction was carried out in refluxing THF (data not shown). At $R_2$ and $R_3$, however, both alkyl- and aryl-type reactants gave crude 3-alkylamino-1,2,4-triazoles in good purity (Table 1). All products were characterized by HPLC, LC-MS, and $^1$HNMR.[18] The typical HPLC chromatogram of the 3-alkylamino-1,2,4-triazole products is depicted in Figure 1.

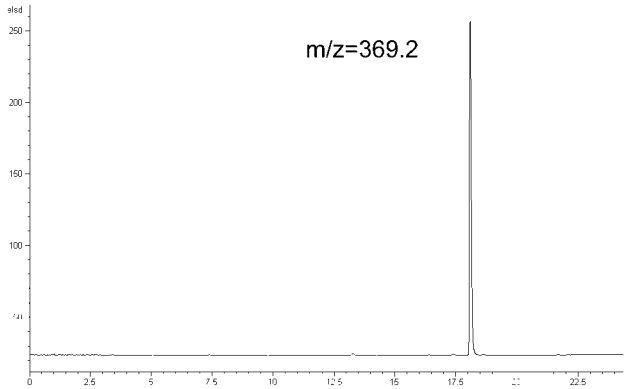



**Figure 1.** Typical HPLC chromatogram of crude 3-alkylamino-triazoles (**6c** shown) synthesized according to the procedure in Scheme 1.

The yields were good for reactions where $R_3$ was a methyl group and moderate for benzylic or aryl hydrazines, a result of the formation and premature cleavage of the corresponding 3-benzotriazole-substituted 1,2,4-triazole byproducts (**7**). A sharp single peak for the correct ion in two different HPLC methods confirmed complete regioselectivity for the formation of the aminotriazole products. In addition, $^1$HNMR spectra of purified representative analogues **6a** and **6f** (and of all other crude **6** triazoles in Table 1) indicated the presence of a single isomer as well. Aminotriazoles prepared regioselectively by the similar solution-phase method have been shown by X-ray crystallography to be the 3-alkylamino isomers.[13]

In conclusion, we demonstrated a method for the solid-phase synthesis of benzotriazole-1-carboximidamides as well as *N*-acyl-benzotriazole-1-carboximidamides and the utility

(18) **$^1$H NMR Data for Compounds in Table 1. 6a**: 400 MHz, acetone-$d_6$ $\delta$ 7.72 (d, 2H), 7.43 (d, 2H), 7.31 (d, 2H), 7.17 (d, 2H), 4.43 (s, 2H), 3.94 (s, 3H), 2.43 (s, 3H), 2.33 (s, 3H). **6c**: 400 MHz, DMSO-$d_6$ $\delta$ 7.42 (d, 2H), 7.30−7.08 (m, 11H), 5.12 (s, 2H), 4.14 (s, 2H), 2.36 (s, 3H), 2.25 (s, 3H). **6d**: 400 MHz, acetone-$d_6$ $\delta$ 7.37 (m, 6H), 7.22 (d, 2H), 7.15 (d, 2H), 7.02 (d, 2H), 4.45 (s, 2H), 3.84 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H). **6e**: 400 MHz, acetone-$d_6$ $\delta$ 3.85 (s, 3H), 3.20 (m, 1H), 3.02 (d, 2H), 2.05−1.15 (m, 10H), 0.98 (d, 6H), 0.90 (m, 1H). **6f**: 400 MHz, DMSO-$d_6$ $\delta$ 7.41 (s, 5H), 5.55 (s, 2H), 3.30 (m, 1H), 3.04 (d, 2H), 1.90−1.60 (m, 6H), 1.43−1.23 (m, 4H), 0.98 (d, 6H), 0.90 (m, 1H). **6g**: 400 MHz, acetone-$d_6$ $\delta$ 7.58 (d, 2H), 7.15 (d, 2H), 3.93 (s, 3H), 3.08 (d, 2H), 2.88 (m, 1H), 2.00−1.63 (m, 6H), 1.287 (m, 4H), 0.98 (d, 6H), 0.90 (m, 1H).

thereof in the solid-phase synthesis of 3-alkylamino-1,2,4-triazoles. The title compounds were prepared with complete control over regioselectivity and in high purity. Our ongoing efforts for the synthesis of other alkylamino-heterocyclic systems starting from intermediate **3** will be reported elsewhere.

**Acknowledgment.** The authors thank Ling Morgan (NeoGenesis) for her contribution to the purification of aminotriazole compounds for $^{1}$HNMR and Steve Adams (NeoGenesis) for his critical assessment of the manuscript.

OL025821I