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Solid-phase synthesis of 3-amino-1,2,4-triazoles

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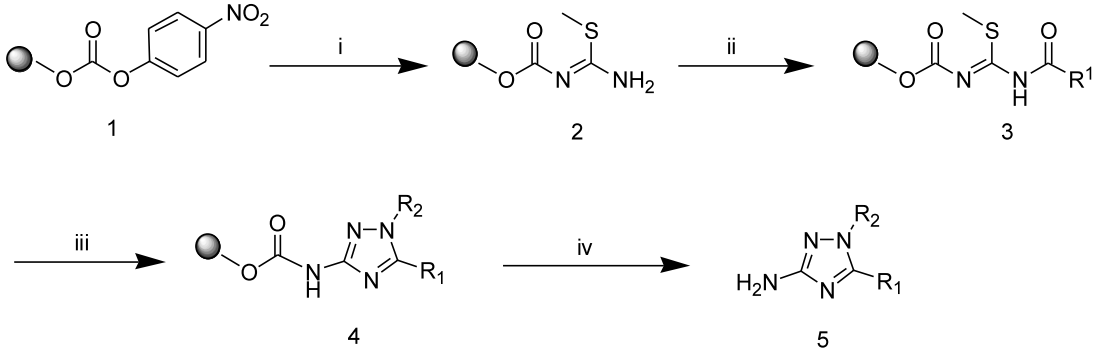
Abstract—A solid-phase synthesis of 3-amino-1,2,4-triazoles is described. Reaction of resin bound *S*-methylisothiourea **2** with carboxylic acids yielded resin-bound *S*-methyl-*N*-acylisothioureas **3**, which reacted with hydrazines under mild conditions to afford the corresponding resin-bound 3-amino-1,2,4-triazoles **4** with regioselectivity. Following cleavage, the desired products **5** were obtained in good yields and purities.

Combinatorial chemistry has emerged as a powerful methodology for the preparation of libraries of small organic compounds in order to accelerate the drug discovery process.[1] Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. As a result, an increasing range and number of pharmaceutically useful heterocyclic compounds recently have been prepared using solid-phase methodology.[2] This approach permits the rapid synthesis of large numbers of individual compounds, as well as mixture-based combinatorial libraries in a short time frame and facilitates their use in high-throughput screening.[3] Aminotriazoles are found in many biologically active compounds and are known to have useful therapeutic implications.[4] 3-Aminotriazoles have been found effective for the treatment of chronic bronchial asthma.[5]

Recently, several reports have described solid-phase syntheses of triazole derivatives.[6] As part of our ongoing efforts directed toward the solid-phase synthesis of small molecule and heterocyclic compounds and the generation of combinatorial libraries of organic compounds,[7] we report here an efficient strategy for the solid-phase synthesis of 3-amino-1,2,4-triazoles.

The parallel solid-phase synthesis of 3-amino-1,2,4-triazoles was carried out on the solid phase using the 'tea-bag' methodology.[8] The reaction sequence is illustrated in Scheme 1.

Starting from *p*-nitrophenylcarbonate resin **1**, *S*-methylisothiouronium sulfate was attached to the resin in the presence of cesium carbonate in DMF.[9] The resin-bound *S*-methylisothiourea **2** was reacted with a



Scheme 1. Solid-phase synthesis of 3-amino-1,2,4-triazoles **5**. *Reagents and conditions*: (i) *S*-methylisothiouronium sulfate (6 equiv., 0.1 M), Cs_2CO_3 (12 equiv., 0.2 M) in DMF, rt, 48 h; (ii) R^1COOH (10 equiv., 0.1 M), DIC (10 equiv., 0.1 M), HOBt (10 equiv., 0.1 M) in DMF, rt, overnight; (iii) R^2NHNH_2 (6 equiv., 0.1 M) in DMF, 40°C, overnight; (iv) TFA/DCM (1:1), 1 h.

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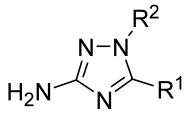
carboxylic acid to yield the corresponding *S*-methyl-*N*-acylisothioureas **3**. Condensation of resin-bound *S*-methyl-*N*-acylisothioureas **3** with hydrazines overnight at 40°C led to the displacement of the methylthio group and cyclization to give the resin-bound products **4**. The desired 3-amino-1,2,4-triazoles **5** were cleaved from the resin using 50% trifluoroacetic acid in dichloromethane for 1 h in good yield and high purity.[10] The results are summarized in Table 1. From these results, independent of the nature of the R^1 substituent, resin-bound imi-

Table 1. Individual 3-amino-1,2,4-triazoles



Entry	Product	R^1	R^2	Yield[a]	Purity[b]	MW (found)[c]
1	**5a**	3,5-$(CF_3)_2$ $C_6H_4CH_2$	C_6H_5	62	82	387.7 ($[M+H]^+$)
2	**5b**	$C_6H_4CH_2$	C_6H_5	65	85	251.2 ($[M+H]^+$)
3	**5c**	3-$FC_6H_4CH_2$	C_6H_5	63	83	269.6 ($[M+H]^+$)
4	**5d**	3-$FC_6H_4CH_2$	H	71	79	193.2 ($[M+H]^+$)
5	**5e**	4-$FC_6H_4CH_2$	C_6H_5	68	82	269.6 ($[M+H]^+$)
6	**5f**	4-$CH_3C_6H_4$	C_6H_5	58	80	251.1 ($[M+H]^+$)
7	**5g**	4-$CH_3C_6H_4$	H	65	83	175.2 ($[M+H]^+$)
8	**5h**	$(CH_3)_2CH$	C_6H_5	73	88	203.2 ($[M+H]^+$)
9	**5i**	$(CH_3)_2CHCH_2$	C_6H_5	63	74	217.3 ($[M+H]^+$)
10	**5j**	4-$CH_3CH_2OC_6H_4CH_2$	H	59	87	219.3 ($[M+H]^+$)
11	**5k**	4-$CH_3CH_2OC_6H_4CH_2$	C_6H_5	62	79	295.8 ($[M+H]^+$)
12	**5l**	4-$NO_2C_6H_4(CH_2)_3$	H	75	82	248.2 ($[M+H]^+$)
13	**5m**	$C_6H_5(CH_2)_3$	H	68	86	203.3 ($[M+H]^+$)

[a] Percent yields are based on the weight of crude material and are relative to the initial loading of the resin.
[b] The purity of the crude material was estimated based on analytical traces at $\lambda = 214$ nm.
[c] Confirmed by mass spectrometry (ESI).

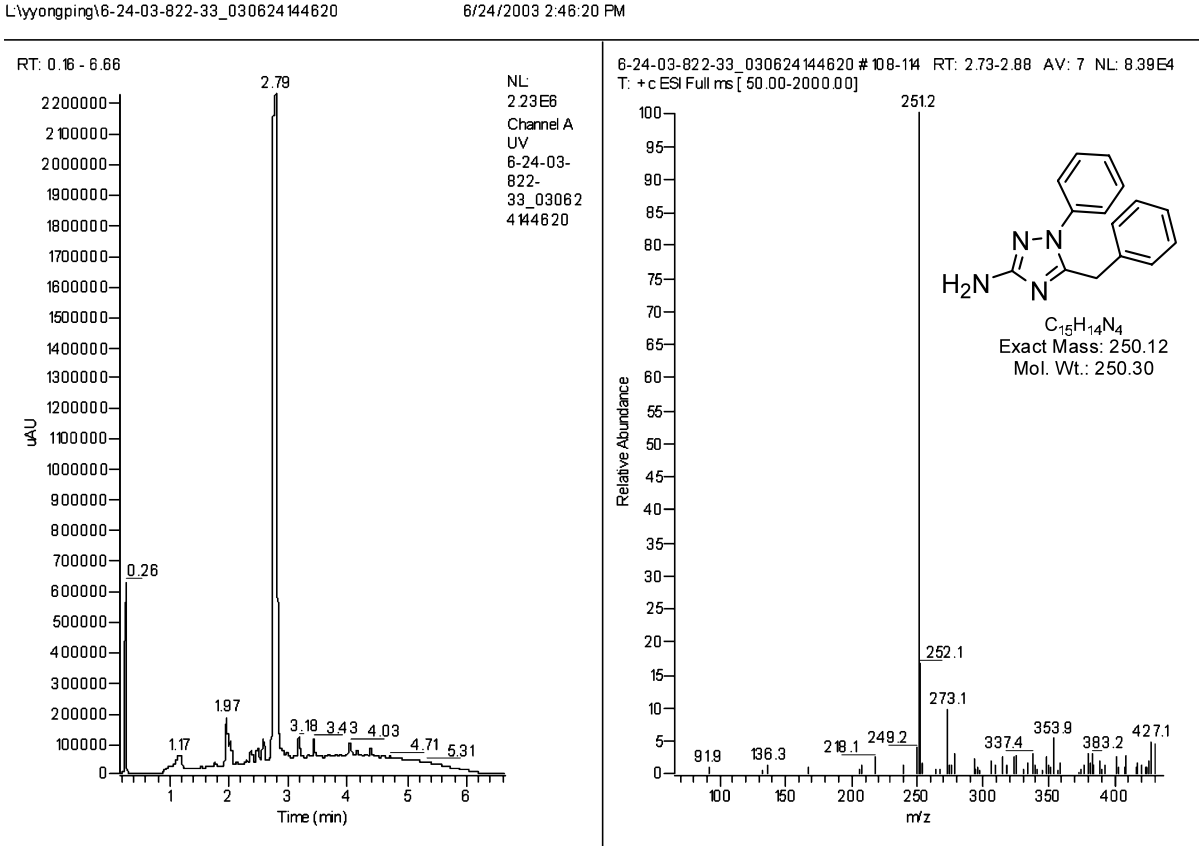


Figure 1. LC-MS of crude **5b**.

noureas **3**, both alkyl and aryl R^1 groups of **3** gave products in good purities. ^{1}H NMR and HPLC of products demonstrated the presence of a single isomer and the cyclization are regioselective as previously reported.[6c,11] It is expected that the lower yield found was due to substitution of the methyl thio group by hydrazine, followed by cyclization and concomitant cleavage upon reaction of the hydrazino group with the urethane carbonyl. Figure 1 illustrates a typical LC-MS spectrum of crude product of **5b**.

In conclusion, we have demonstrated an efficient approach for the parallel solid-phase synthesis of substituted 3-amino-1,2,4-triazoles from common building blocks, such as carboxylic acids (R^1) and hydrazines (R^2).

Acknowledgements

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10. **General procedure for the synthesis of substituted 3-amino-1,2,4-triazoles**: 77 mg of *p*-nitrophenylcarbonate resin (1.3 mmol/g, 100–200 mesh, 1% DVB) was sealed within a polypropylene mesh packet. Reactions were carried out in polypropylene bottles. To the resin was in 6 ml dry dimethylformamide (DMF), *S*-methylisothiouronium sulfate (166 mg, 6 equiv., 0.1 M) and Cs_2CO_3 (390 mg, 12 equiv., 0.2 M) was added and the reaction was shaken for 48 h at room temperature, followed by washes with DMF (three times), DCM (twice) and methanol (three times). The resulting resin-bound **2** was treated with a carboxylic acid (10 equiv., 0.1 M) in DMF overnight using DIC (10 equiv., 0.1 M) and HOBt (10 equiv., 0.1 M) as coupling reagent to yield the resin-bound *S*-methyl-*N*-acylisothioureas **3**. The resin was washed with DMF (three times), DCM (twice) and methanol (three times). The resin-bound compound **3** was reacted with a hydrazine (6 equiv., 0.1 M) in DMF at 40°C overnight to afford the resin-bound 3-amino-1,2,4-triazoles **4**. After washing with DMF (three times), CH_2Cl_2 (three times) and MeOH (three times), the resin was cleaved with 50% trifluoroacetic acid in dichloromethane for 1 h to give the corresponding crude product **5**. The product was characterized by electrospray LC-MS under ESI conditions. Following purification by RP-HPLC, the identity of the compounds was confirmed by ^{1}H NMR. 5-(3,5-Bis-trifluoromethyl-benzyl)-1-phenyl-1*H*-[1,2,4]-triazol-3-ylamine (**5a**): LC-MS (ESI) m/z 387.7 ($M+H^+$). ^{1}H NMR (500 MHz, DMSO): δ 4.35 (s, 2H), 7.41–7.95 (m, 8H).
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