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Solid-phase synthesis of 5-aminotetrazoles

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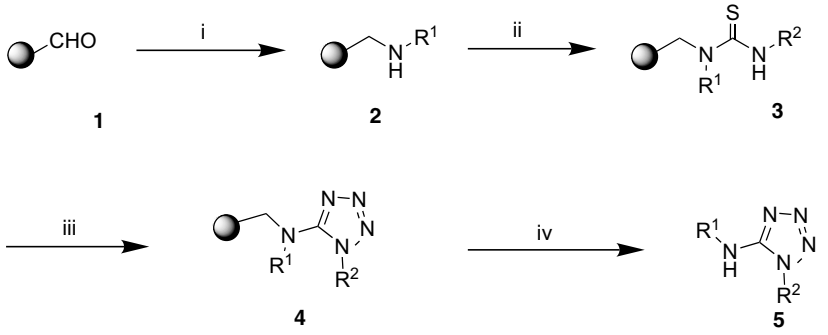
Abstract—A solid-phase synthesis of 5-aminotetrazoles is described. Resin-bound thioureas were displaced by sodium azide in the presence of $HgCl_2$ and following nucleophilic cyclization produced the resin-bound products. The desired 5-aminotetrazoles were cleaved from the resin using 95% trifluoroacetic acid in dichloromethane in good yield and purity.

The rapid synthesis of large organic compound collections by combinatorial methods using solid-phase and solution-phase approaches facilitate the discovery of pharmaceutical lead compounds.[1] These approaches enable the synthesis of large numbers of individual compounds as well as mixture-based combinatorial libraries for use in high-throughput screening.[2] 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 have been prepared using solid-phase methodologies.[3] There is considerable interest in the medicinal and biological applications of tetrazoles,[4] including 5-aminotetrazoles, due to their reported anti-allergic,[5] antiviral,[6] and cognition disorder activities.[7]

Recently, several reports have described syntheses of 5-aminotetrazoles using azide anion in solution.[8] As part of our ongoing efforts directed toward the solid-phase synthesis of small molecule heterocyclic compounds and the generation of combinatorial libraries,[9] we report here an efficient strategy for the solid-phase synthesis of 5-aminotetrazoles.

The parallel solid-phase synthesis of 5-aminotetrazoles was carried out on the solid-phase using the 'teabag' methodology.[10] The reaction sequence is illustrated in Scheme 1.



Scheme 1. Solid-phase synthesis of 5-aminotetrazoles **5**. Reagents and conditions: (i) R^1NH_2 (6 equiv, 0.1 M), $NaBH(OAc)_3$ (6 equiv, 0.1 M) in DMF/AcOH (99:1), rt, overnight; (ii) R^2NCS (6 equiv, 0.1 M) in DCM, rt, overnight; (iii) NaN_3 (6 equiv, 0.1 M), $HgCl_2$ (6 equiv, 0.1 M) in DMF, rt, overnight; (iv) TFA/DCM (95:5), 1 h.

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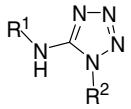
Table 1. Individual 5-aminotetrazoles



Entry	Product	R^1	R^2	Yield[a]	Purity[b]	MW (found)[c]
1	**5a**	$C_6H_5CH_2CH_2$	4-$CH_3OC_6H_4$	68	83	295.1 ([M + Na]$^+$)
2	**5b**	$C_6H_5CH_2CH_2$	3-FC_6H_4	75	81	283.3 ([M + H]$^+$)
3	**5c**	$C_6H_5CH_2CH_2$	CH_3CH_2	63	83	217.2 ([M + H]$^+$)
4	**5d**	4-$CH_3OC_6H_4CH_2$	4-$CH_3OC_6H_4$	71	79	311.3 ([M + H]$^+$)
5	**5e**	4-$CH_3OC_6H_4CH_2$	CH_3CH_2	75	86	233.3 ([M + H]$^+$)
6	**5f**	4-$FC_6H_4CH_2CH_2$	CH_3CH_2	62	82	235.3 ([M + H]$^+$)
7	**5g**	2-$CF_3C_6H_4CH_2$	C_6H_5	73	85	319.3 ([M + H]$^+$)
8	**5h**	2-$CF_3C_6H_4CH_2$	CH_3CH_2	71	78	271.2 ([M + H]$^+$)
9	**5i**	3-$CF_3C_6H_4CH_2$	C_6H_5	65	81	319.3 ([M + H]$^+$)
10	**5j**	3-$CF_3C_6H_4CH_2$	CH_3CH_2	61	78	217.2 ([M + H]$^+$)
11	**5k**	$CH_3CH_2CH_2CH_2$	C_6H_5	67	77	217.2 ([M + H]$^+$)
12	**5l**	$CH_3CH_2CH_2CH_2$	4-$CH_3OC_6H_4$	72	82	247.3 ([M + H]$^+$)
13	**5m**	$CH_3CH_3NCH_2CH_2$	C_6H_5	68	76	232.1 ([M + H]$^+$)
14	**5n**	$CH_3OCH_2CH_2$	C_6H_5	72	81	219.1 ([M + H]$^+$)
15	**5o**		2-FC_6H_4	69	83	263.1 ([M + H]$^+$)
16	**5p**		C_6H_5	72	78	257.2 ([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 spectra (ESI).

Starting from 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin **1**, reductive amination was used to attach a primary amine to the resin in the presence of $NaBH(OAc)_3$ in DMF. The resin-bound amine **2** was then reacted with an isothiocyanate to yield the corresponding thiourea **3**. The mercury-activated thiourea was displaced by sodium azide and subsequent intramolecular nucleophilic cyclization gave the resin-bound products **4**. The resulting desired 5-aminotetrazoles **5** were cleaved from the resin with 95% trifluoroacetic acid in dichloromethane for 1 h in good yield and purity.[11] The results are summarized in Table 1. The results show

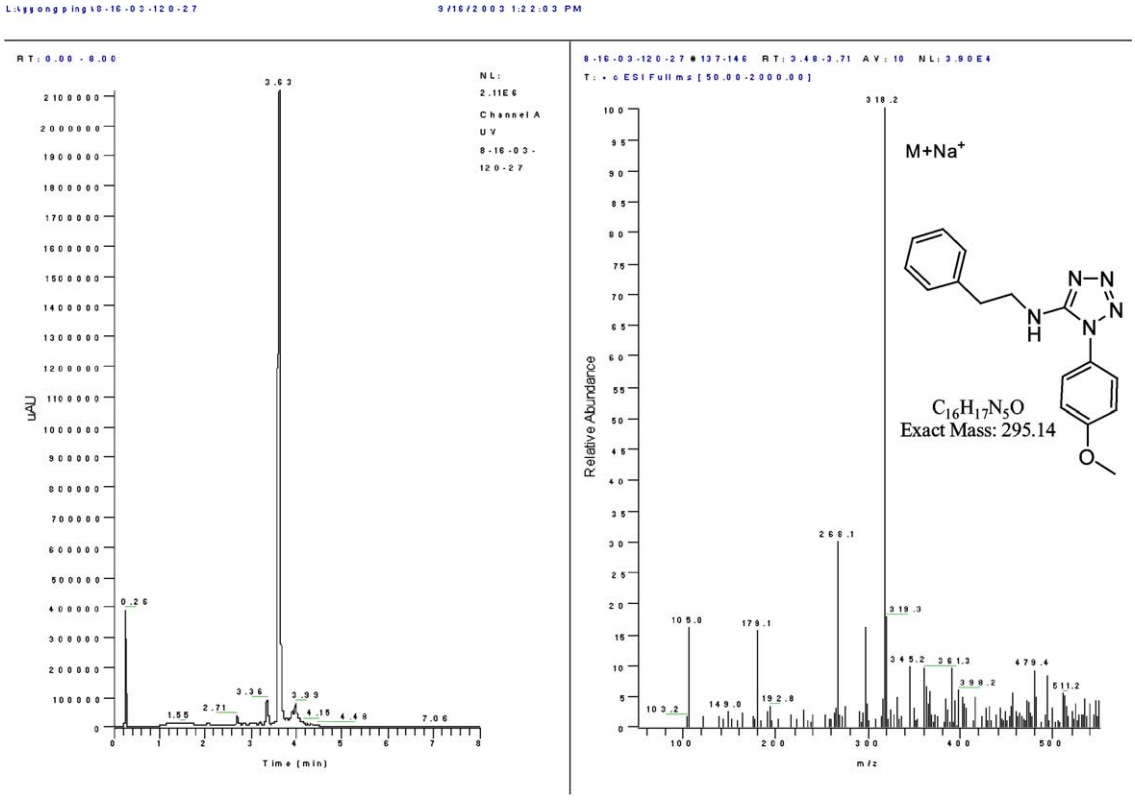


Figure 1. LC–MS of crude **5a**.

that either alkyl or aryl R^2 groups on **3** gave products in good purity independent of the nature of the R^2 substituent Figure 1 illustrates a typical LC–MS spectrum of crude product **5a**.

In conclusion, we have demonstrated an efficient approach for the parallel solid-phase synthesis of disubstituted 5-aminotetrazoles from readily available amines (R^1) and isothiocyanates (R^2) building blocks.

Acknowledgements

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11. *General procedure for the synthesis of disubstituted 5-aminotriazoles*: 110 mg of 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin (0.89 mmol/g, 100–200 mesh, 1% DVB, Novabiochem, San Diego) was sealed within a polypropylene mesh packet. Reactions were carried out in polypropylene bottles. A solution of $NaBH(OAc)_3$ (6 equiv, 0.1 M) in 6 mL DMF containing 1% AcOH was added to the resin, followed by the addition of an amine (6 equiv, 0.1 M). The reaction was shaken at room temperature overnight, followed by washes with DMF (three times), DCM (two times) and methanol (three times). The resulting resin-bound **2** was treated with an isothiocyanate (6 equiv, 0.1 M) in DCM overnight to yield the resin-bound thioureas **3**. The resin was washed with DMF (three times), DCM (two times), and methanol (three times). Resin-bound compound **3** was reacted with sodium azide (6 equiv, 0.1 M) and mercury chloride (6 equiv, 0.1 M) in DMF at room temperature overnight to afford the resin-bound 3-aminotetrazole **4**. After washing with DMF (three times), DCM (three times), and MeOH (three times), the resin was cleaved with 95% 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. Figure 1 illustrates a typical LC–MS spectrum of crude product **5a**. Following purification by RP-HPLC, the identity of the compounds was confirmed by ^1H NMR. [1-(4-Methoxy-phenyl)-1H-tetrazole-5-yl]-phenethylamine **(5a)**: LC–MS (ESI) *m/z* 318.2 ($M + Na^+$). ^1H NMR (500 MHz, DMSO): δ 2.87 (2H, t, $J = 7.8$), 3.45–3.49 (2H, m), 3.83 (s, 3H), 7.12–7.14 (2H, m), 7.18–7.22 (3H, m), 7.28–7.31 (2H, m), 7.40–7.42 (2H, m). ^{13}C NMR (DMSO, 125 MHz): δ 34.7, 45.1, 55.6, 114.9, 125.7, 126.1, 126.5, 128.3, 128.7, 139.2, 155.1, 159.9.