JOURNAL OF combinatorial CHEMISTRY

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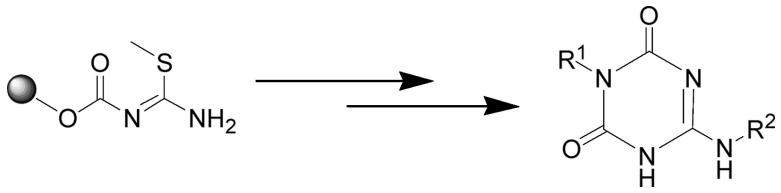
J. Comb. Chem., **2004**, 6 (1), 83-85• DOI: 10.1021/cc030017o • Publication Date (Web): 01 November 2003



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A Traceless Approach for the Solid-Phase Synthesis of 6-Amino-1,3,5-triazine-2,4-diones

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Received February 25, 2003

A traceless approach for the solid-phase synthesis of 6-amino-1,3,5-triazine-2,4-diones is described. Reaction of resin-bound *S*-methylisothiourea with isocyanates yielded resin-bound iminoureas **3**, which reacted with amines to afford the corresponding guanidines **4**. Following intramolecular cyclizative cleavage of the resin-bound guanidines using potassium ethoxide as a base, the desired products **5** were obtained in good yields and high 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]. 1,3,5-Triazines are found in many biologically active compounds and are known to have useful therapeutic implications.[4] The guanidine group has attracted attention in the field of medicinal chemistry due to the hydrogen-bonding acceptor and donor abilities of the guanidino group playing important roles in supramolecule formation and in bioactive substances. Compounds containing the guanidine moiety are present in several marketed drugs or drug candidates.[5]

Recently, several papers have described solid-phase syntheses of different triazine derivatives utilizing chlorocarbonyl isocyanate cyclization chemistry.[6] However, one of the challenges of the solid-phase combinatorial synthesis of heterocyclic compounds is developing chemical routes that provide access to the target compounds without leaving any trace of the linker used for tethering the starting building blocks to the solid support.[7] 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,[8] we report here a traceless approach for the solid-phase synthesis of 6-amino-1,3,5-triazine-2,4-diones.

The parallel solid-phase synthesis of 6-amino-1,3,5-triazine-2,4-diones was carried out on the solid phase using the "tea bag" methodology.[9] The reaction sequence is illustrated in Scheme 1.

Starting from *p*-nitrophenyl carbonate resin **1**, *S*-methylisothiouronium sulfate was coupled to the resin in the presence of cesium carbonate in dimethyl formamide (DMF).[10] The resin-bound *S*-methylisothiourea **2** was reacted with an isocyanate to yield the corresponding iminourea **3**. Reaction of this resin-bound compound **3** with an amine led to the displacement of the methylthio group to give the resin-bound guanidine **4**. The desired 6-amino-1,3,5-triazine-2,4-diones **5** were obtained via intramolecular cyclization with concomitant cleavage from the resin using potassium ethoxide as a base at 60 °C overnight in good yield and high purity. The results are summarized in Table 1.

From these results, independent of the nature of the substituent R^1 resin-bound iminoureas **3**, reactions of **2** with both alkyisocyanates and arylisocyanates gave products in good purities. The electron-donating and electron-withdrawing groups on the arylisocyanates also gave similar results (entries **5a**,**f**). The conversion of the corresponding resin-bound guanidines **4** was achieved by reaction of resin-bound iminoureas **3** with primary amines in tetrahydrofuran (THF) overnight at 50 °C. However, secondary amines (such as piperidine, *N*-ethylmethylamine, and *N*-benzylmethylamine) cleaved the resin-bound iminoureas **3** and were excluded from use as building blocks. Aniline did not react sufficiently to generate resin-bound guanidines **4**. Only a trace of desired product was observed under these reaction conditions. For evaluation of the reaction, compound **6** was cleaved from the solid support by treatment with 50% trifluoroacetic acid in methylene chloride. For the intramolecular cyclization and cleavage of resin-bound **4** into product **5**, we found only a trace of product **5**, as well as the uncyclized byproduct **6**, which was observed in the liquid chromatography−mass spectrometry (LC-MS) when the resin was treated at elevated temperature (60−110 °C) without the use of a base. Treatment with K_2CO_3 gave a low yield of product **5**. Successful intramolecular cycli-

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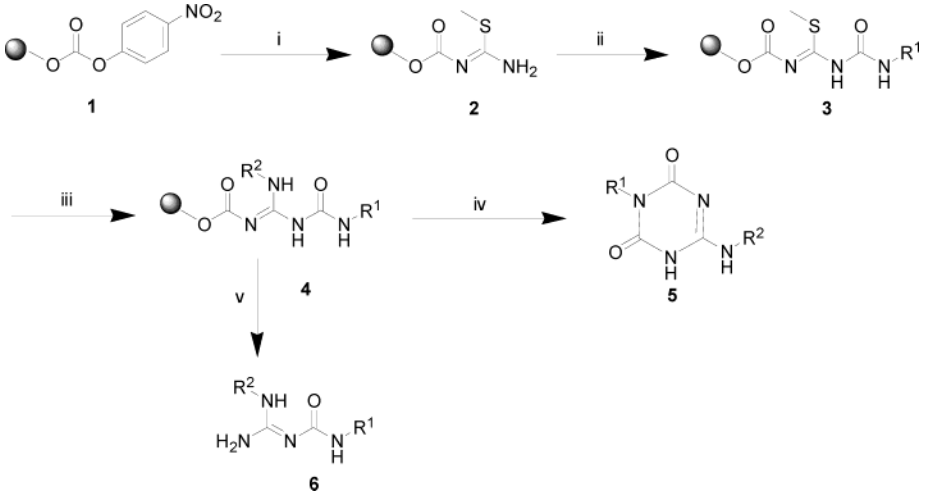
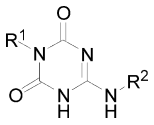
10.1021/cc030017o CCC: $27.50
Published on Web 11/01/2003

Scheme 1. Solid-Phase Synthesis of 6-Amino-1,3,5-triazine-2,4-diones **5**[a]



[a] Reagents and conditions: (i) *S*-methylisothiouronium sulfate (6 equiv, 0.1 M), Cs_2CO_3 (12 equiv, 0.2 M) in DMF, room temperature, 48 h. (ii) R^1NCO (6 equiv, 0.1 M) in DCM, room temperature, overnight. (iii) R^2NH_2 (6 equiv, 0.1 M) in THF, 50 °C, overnight. (iv) KOEt (3 equiv, 0.1 M) in EtOH, 60 °C, overnight. (v) TFA/DCM (1:1), 1 h.

Table 1. Individual 6-Amino-1,3,5-triazine-2,4-diones



entry	product	R^1	R^2	yield[a]	purity[b]	MW (found)[c]
1	**5a**	4-$CH_3OC_6H_4$	$(CH_3)_2CHCH_2$	82	91	291.2 ($[M + H]^+$)
2	**5b**	4-$CH_3C_6H_4$	2-$CH_3OC_6H_4CH_2$	85	86	339.1 ($[M + H]^+$)
3	**5c**	$CH_3CH_2CH_2$	4-$CH_3C_6H_4CH_2$	83	92	275.1 ($[M + H]^+$)
4	**5d**	$CH_3(CH_2)_4CH_2$	2-$CH_3OC_6H_4CH_2$	82	90	333.4 ($[M + H]^+$)
5	**5e**	4-$CH_3OC_6H_4$	3-$ClC_6H_4CH_2CH_2$	88	92	373.2 ($[M + H]^+$)
6	**5f**	4-FC_6H_4	$CH_3OCH_2CH_2CH_2$	78	90	295.1($[M + H]^+$)
7	**5g**	C_6H_5	$C_6H_5CH_2CH_2$	85	93	309.2 ($[M + H]^+$)
8	**5h**	4-FC_6H_4	$(CH_3)_2CHCH_2$	81	88	279.2 ($[M + H]^+$)
9	**5i**	4-$CH_3C_6H_4$	$CH_3OCH_2CH_2CH_2$	83	89	291.2 ($[M + H]^+$)
10	**5j**	$CH_3CH_2CH_2$	$C_6H_5CH_2CH_2$	79	87	275.2 ($[M + H]^+$)
11	**5k**	$CH_3CH_2CH_2$	2-$CH_3OC_6H_4CH_2$	88	91	291.1 ($[M + H]^+$)
12	**5l**	$C_6H_5CH_2$	2-$CH_3OC_6H_4CH_2$	85	92	339.1 ($[M + H]^+$)
13	**6a**	C_6H_5	$C_6H_5CH_2CH_2CH_2$	88	91	297.2 ($[M + H]^+$)

[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).

zation and cleavage of **4** was accomplished by treatment with KOEt in EtOH overnight at 60 °C in good yield and high purity.

In conclusion, we have demonstrated a novel traceless approach for the parallel solid-phase synthesis of substituted 6-amino-1,3,5-triazine-2,4-diones from common building blocks, such as isocyanates (R^1) and amines (R^2). In addition, the reaction conditions are readily amenable to the synthesis of individual and mixture-based combinatorial libraries.

Acknowledgment. This work was supported by National Cancer Institute Grant No. CA78040 (Houghten).

Supporting Information Available. Experimental procedures and ^1H NMR and LC-MS spectra for all products and ^{13}C NMR of compounds **5a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC030017O