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Reaction of isothiourea with 2,3-diaza-3-pentenedioic anhydride. A solid-phase synthesis of 3-amino-1,2,4-triazin-5(4*H*)-ones

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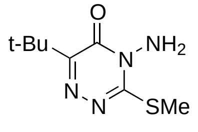
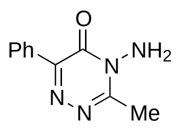
Abstract—The first reported solid-phase synthesis of 3-amino-1,2,4-triazin-5(4*H*)-ones is described. Reactions of polymer-bound isothiourea with 2,3-diaza-3-pentenedioic anhydride forms 3-amino-1,2,4-triazin-5(4*H*)-ones in good yields and high purity. © 2001 Elsevier Science Ltd. All rights reserved.

Solid-phase syntheses of small, organic molecules have received widespread attention during the last decade.[1] In particular, a large number of heterocycles have been synthesized using many of these solid-phase approaches.[2] 1,2,4-Triazin-5-one is a very important class of heterocyclic compounds that show a wide variety of applications in both the pharmaceutical and agrochemical industries. As potential human therapies, 1,2,4-triazin-5-ones have exhibited anticancer,[3] antiulcer[4] and antiinflammatory[5] effects. Within the agrochemical field, this class of compound has shown activity as herbicides,[6–8] desiccants,[7] defoliants,[7] plant-growth regulators[7] and insecticides.[8] There is also a report of this compound class increasing crop yields.[9] Examples of herbicidal 1,2,4-triazin-5-ones include metribuzin (**1**) and metamitron (**2**).[10]

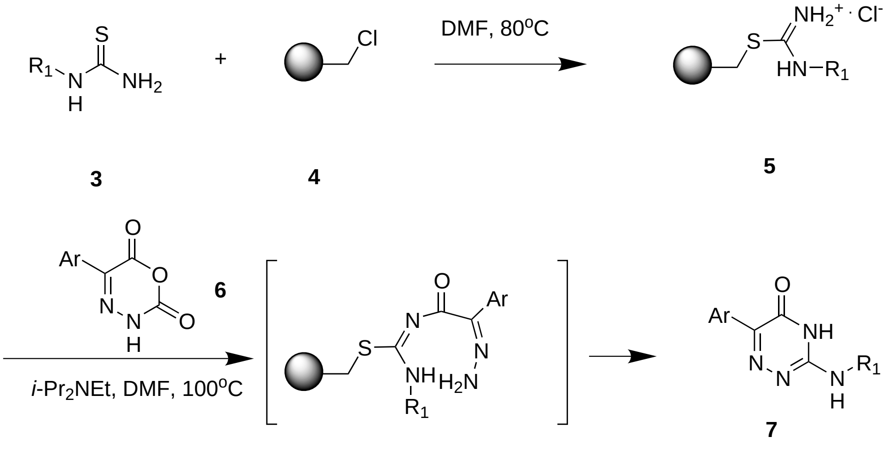


Metribuzin (**1**)



Metamitron (**2**)

Despite the importance of this compound class, there are no published reports of a solid-phase synthesis of 1,2,4-triazin-5-ones. Recently, we reported a concise and efficient solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones via the reaction of polymer-bound



Scheme 1.

Keywords: solid-phase synthesis; thioformamidines; triazinones.

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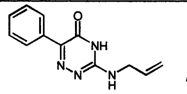
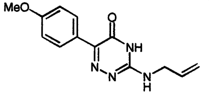
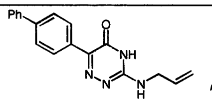
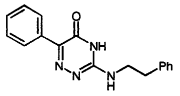
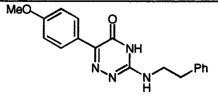
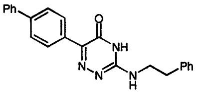
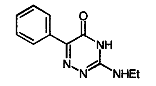
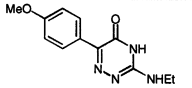
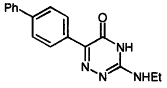
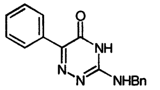
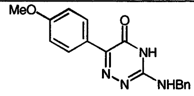
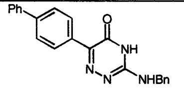
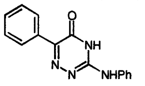
isothiourea **5** with isatoic anhydride.[11] As part of our continuing interest in the synthesis of biologically relevant heterocycles from polymer-bound isothiourea, herein we report a convenient traceless solid-phase synthesis of 3-amino-1,2,4-triazin-5(4*H*)-ones.

The polymer-bound isothiourea **5**, prepared quantitatively from the reaction of thiourea **3** and chloromethyl polystyrene resin **4** (2% DVB Merrifield resin, 2.3 mmol/g) in DMF at 80°C,[11] is reacted with a stoichiometric amount of 2,3-diaza-3-pentenedioic anhydride **6**[12] in DMF in the presence of diisopropylethylamine at 100°C. The expected product, 3-amino-1,2,4-triazin-5(4*H*)-one **7**, is obtained (Scheme 1). The products are formed via a similar mechanism as we described previously,[11] i.e. acylation of isothiourea **5** with 2,3-diaza-3-pentenedioic anhydride **6** followed by release of the resulting product **7** via an intramolecular cyclization. The results summarized in Table 1 indicate that the reaction is general for *N*-alkyl-substituted isothioureas. *N*-Phenyl-substituted isothiourea, though, fails to provide the desired product in good purity (entry 13 in

Table 1. Solid-phase synthesis of 3-amino-1,2,4-triazin-5-ones **7**

Entry	Product 7	Yield[a]	Purity[b]	MS (M+H$^+$)
1	 **7a**	50%	95%	229
2	 **7b**	74%	83%	259
3	 **7c**	75%	91%	305
4	 **7d**	95%	91%	293
5	 **7e**	71%	90%	323
6	 **7f**	74%	82%	369
7	 **7g**	58%	87%	217
8	 **7h**	52%	84%	247
9	 **7i**	72%[c]	85%	293
10	 **7j**	64%	71%	279
11	 **7k**	58%	74%	309
12	 **7l**	65%	67%	355
13	 **7m**	NA[d]	48%	265

a. Isolated yields, calculated based on the quantity of **6** used. b. Purity was determined by HPLC using UV (254 nm) detector. c. Reaction was run in DMSO due to poor solubility of this product in DMF. d. Not isolated

Table 1). We have found that the reactions work well in DMSO too. For example, reaction of *N*-ethylisothiourea with 1-(4-biphenyl)-2,3-diaza-3-pentenedioic anhydride in DMSO gives the desired product in 72% yield with 85% purity (entry 9). All the products are fully characterized by ^{1}H NMR and mass spectrometric techniques.

In summary, we have disclosed a novel reaction of polymer-bound isothiourea with 2,3-diaza-3-pentenedioic anhydride, which provides a very convenient solid-phase synthesis of 3-amino-1,2,4-triazin-5(4*H*)-ones. This is the first reported solid-phase synthesis of 1,2,4-triazin-5-one class of compounds. The products formed using this method are devoid of any residual functionality due to resin attachment (i.e. traceless). Unlike the most commonly used solution-phase methods reported in literature,[13] which liberate methylthiol as a by-product from the reaction of amine with 3-methylthio-1,2,4-triazin-5(4*H*)-one, this solid-phase method releases polymer-bound thiol, thus providing a better working environment, especially for library production.

General procedure: The mixture of polymer-bound isothiourea **5** (0.18 mmol) and 2,3-diaza-3-pentenedioic anhydride **6** (0.15 mmol) was heated in anhydrous DMF (1.0 mL) in the presence of diisopropylethylamine (0.07 mL, 0.4 mmol) at 100°C for 24 h. The resin was filtered and washed with hot DMF (0.5 mL×3), and the combined filtrate was concentrated to give a solid residue. The desired product, 3-amino-1,2,4-triazin-5(4*H*)-ones **7**, was obtained by washing the residue with water (0.5 mL×3).

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