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# A FACILE PREPARATION OF A COMBINATORIAL LIBRARY OF 2,6-DISUBSTITUTED TRIAZINES

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**Abstract:** Thiouronium salts of type **3** as dinucleophiles are excellent precursors for the synthesis of various heterocycles in combination through cyclization with a large variety of electrophiles. Using this strategy, 2,6-disubstituted-[1,3,5] triazines of types **4** and **6** have been prepared in good yields.
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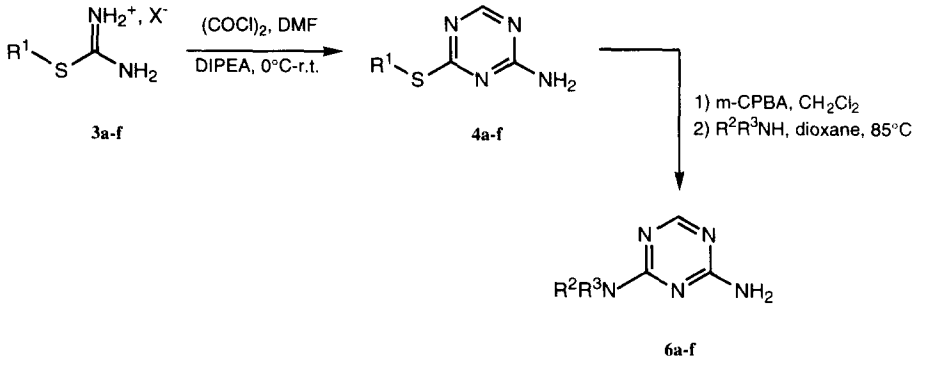
Triazines and their derivatives are of great importance in organic chemistry and have found many applications in the pharmaceutical field. In the past, the preparation of the triazine ring system was one of the main interest within the chemistry of six-membered ring heterocycles. Nowadays, the preparation of triazines is accomplished using both solution- and solid-phase approaches, such as for example: *a*) the general *Bredereck type synthesis* [1], *b*) the rearrangement of pyrimidines [2], *c*) the reaction of nitriles with guanidine [3], *d*) the *substitution of trifluoro- or trichlorotriazines* [4], and *e*) the condensation of S-methylisothioura with *N*-cyanodithioimidocarbonate derivatives [5].

Despite all the existing approaches towards the triazine skeleton, there is still room for new access, especially with regard to parallel and combinatorial chemistry. We present in this paper a facile preparation of 2,6-disubstituted triazines of types **4** and **6** through basic-catalyzed cyclization of the corresponding thiouronium salts (Scheme 1).




**3a-f** **4a-f** **6a-f**

**Scheme 1** : **a:** $R^2$=$R^3$=*N*-Boc piperazine; **b:** $R^2$=tetrahydrofurfurylamine, $R^3$=H; **c:** $R^2$=furfurylamine, $R^3$=H; **d:** $R^2$=2-thiophenethylamine, $R^3$=H; **e:** $R^2$=allylamine, $R^3$=H; **f:** $R^2$=phenethylamine, $R^3$=H.

The required *bis*-nucleophilic thiouronium salts of type **3** were easily accessible as already reported [6] from thiourea **2** and a large variety of alkyl halides in excellent yields.

The synthesis of the triazines **4a-f** was achieved starting from the thiouronium salts **3a-f** in DMF as shown in Scheme 1. Thus, treatment of $(COCl)_2$ with DMF in $CH_2Cl_2$ at 0°C, followed by addition of the corresponding thiouronium salt **3** in the presence of *N*-ethyl diisopropylamine (DIPEA) afforded the triazines **4a-f** [7] in good yields (Table 1).

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**Table 1** : Synthesis of triazines **4a-f**.

| | $R^1$ | **4** (Yield [%]) |
|---|---|---|
| **3a** | *t*Bu | **4a** (61) |
| **3b** | 4-*t*Bu$C_6H_4CH_2$ | **4b** (25) |
| **3c** | *n*$C_6H_{13}$ | **4c** (65) |
| **3d** | 3-N$CC_6H_4CH_2$ | **4d** (40) |
| **3e** | 4-Me$OC_6H_4CH_2$ | **4e** (15) |
| **3f** | $C_6H_5CH_2$ | **4f** (73) |

**Table 2** : Synthesis of triazines **6a-f**.

| | $R^2R^3NH$ | **6** (Yield [%]) |
|---|---|---|
| **4c** | *N*-Boc-piperazine | **6a** (94.5) |
| **4c** | tetrahydrofurfuryl-amine | **6b** (86.5) |
| **4c** | furfurylamine | **6c** (87) |
| **4c** | 2-thiophenethyl-amine | **6d** (87) |
| **4c** | allylamine | **6e** (83) |
| **4c** | phenethylamine | **6f** (79) |

The synthesis of the triazines **6a-f** was achieved in high yield using the following procedure. As already reported [8], compounds of type **4** react directly with amines to afford the corresponding 2-amino analogs. Moreover, we observed that previous oxidation with *m*CPBA in $CH_2Cl_2$ gave the corresponding 2-(alkylsulfinyl)-substituted triazines **5** [9], which upon treatment with various amines afforded, after FC [10], the products **6a-f** [11] in excellent yields (Table 2).

The presented strategy allows us to synthesize various 2, 6-disubstitued triazines **4** and **6** as shown in Scheme 1. This approach feature thiouronium salt as a useful source for masked sulfur, which can be selectively oxidized. Since 2-alkylsulfinyl [1,3,5] triazines can be easily substituted in various ways, our approach constitutes a novel and efficient synthesis to 2,6-disubstituted triazines. Applications towards the synthesis of biologically interesting triazines using this strategy will be reported in due course.

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## References and notes

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7 **4f** : IR (KBr) : 3280w, 1630s, 1610s, 1470m, 760m, 690m. $^1$H NMR ((D$_6$)DMSO, 250 MHz) : 8.25 (s, 1H arom.) ; 7.65 (br.s, $NH_2$) ; 7.40.7.10 (m, 5H arom.) ; 4.33 (s, 2H aliph.). MS : 219 ([M+H]$^+$, 100), 200 (20).
8 Simig, G.; Van Der Plas, H. C.; Landheer, C. A. *Recl. Trav. Chim. Pays-Bas*, **1976**, *95*, 113.
9 **5c** : IR (KBr) : 3330m, 1676s, 1575s, 1514s, 1062s. $^1$H NMR ((D$_6$)DMSO, 250 MHz) : 8.54 (s, 1H arom.); 8.25 (br.s, $NH_2$); 3.10-2.95 (m, 2H aliph.); 1.75-1.65 (m, 1H aliph.); 1.60-1.25 (m, 7H aliph.); 0.90-0.85 (t, 3 H aliph.). MS : 228 (M$^+$, 10), 211 (20), 181 (15), 165 (40), 144 (100), 123 (30), 96 (40), 68 ((35), 43 (75).
10 Still, W. C.; Kahn, M.; Mitra, A., *J. Org. Chem.* **1978**, *43*, 2923.
11 **6f** : IR (KBr) : 3120w, 1671m, 1564s, 812s, 747m. $^1$H NMR ((D$_6$)DMSO, 250 MHz) : 8.05 (s, 1H arom.); 7.35-7.10 (m, 5H arom); 5.35 (br.s, NH); 5.20 (br.s, $NH_2$); 3.70-3.55 (m, 2H aliph.); 2.88 (t, J=6.9Hz, 2H aliph.). MS : 216 ([M+H]$^+$).