Preparation of *N*,*N*-Dimethyl-*N*′-Arylureas Using *S*,*S*-Dimethyl Dithiocarbonate as a Carbonylating Reagent

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Received 8 October 2008; revised 16 October 2008

Abstract: A new, general method for the preparation of *N*,*N*-dimethyl-*N*′-arylureas using *S*,*S*-dimethyl dithiocarbonate as a phosgene substitute is reported. The method has been set up according to four procedures, all including three steps: (1) reaction of *S*,*S*-dimethyl dithiocarbonate with dimethylamine to give *S*-methyl *N*,*N*-dimethylthiocarbamate; (2) halogenation with various halogenating reagents (chlorine, methanesulfenyl chloride, bromine, and methanesulfenyl bromide) to give *N*,*N*-dimethylcarbamoyl chloride or bromide; (3) in situ reaction with primary arylamines. All the target products were obtained in high yields (85–98%; 16 reactions, average yield 93%) and with high purity. Also noteworthy is the recovery of byproducts of industrial interest, namely methanethiol and dimethyl disulfide, with complete exploitation of the reagent *S*,*S*-dimethyl dithiocarbonate.

Key words: ureas, *S*,*S*-dimethyl dithiocarbonate, halodemethylthiolations, halogenations, carbonylations

The *N*,*N*-dimethyl-*N*′-arylurea family of compounds has been known for a long time. Initially (1940), they were developed as industrial total or selective herbicides, and several are currently on the market. Subsequently, they were also used in other agricultural applications.[2–4] There is a considerable amount of literature, especially patents, dealing with a wide variety of procedures for the preparation of *N*,*N*-dimethyl-*N*′-arylureas, and most of the procedures can be classified into five groups: (i) phosgenation of primary arylamines, with the formation of the corresponding aryl isocyanates and their subsequent reaction in situ with anhydrous dimethylamine;[5] (ii) reactions of aryl isocyanates with anhydrous dimethylamine,[6] aqueous dimethylamine,[7] or dimcarb[8] (a liquid reagent resulting from the reaction of anhydrous dimethylamine with carbon dioxide); (iii) reactions of primary arylamines with *N*,*N*-dimethylcarbamoyl chloride;[9] (iv) transamidation of urea with primary arylamines and subsequent transamidation of the resultant products with dimethylamine,[10] transamidation of *N*,*N*′-diarylureas with dimethylamine,[11,12] transamidation of *N*,*N*-dimethylurea with primary arylamines;[11] and (v) oxidative–reductive carbonylation of nitroarenes and dimethylamine with carbon monoxide in the presence of catalysts.[7e,13]

Of the above procedures, the first three (i–iii) are the most widely used, and are of practical interest also for industrial production. They are closely linked, as aryl isocyanates and *N*,*N*-dimethylcarbamoyl chloride are, in the vast majority of cases, obtained by phosgenation of primary arylamines and dimethylamine, respectively. Therefore, common to all three methods is the use of phosgene,[14] which is a great disadvantage, as phosgene is a reagent that is highly toxic, hazardous to handle, and also leads to serious environmental problems, especially in large-scale production. The other procedures (iv, v) have the advantage of not using phosgene, but they often have other disadvantages, such as drastic reaction conditions (high temperatures or high pressures), limited yields, and difficulty in purifying the obtained ureas.

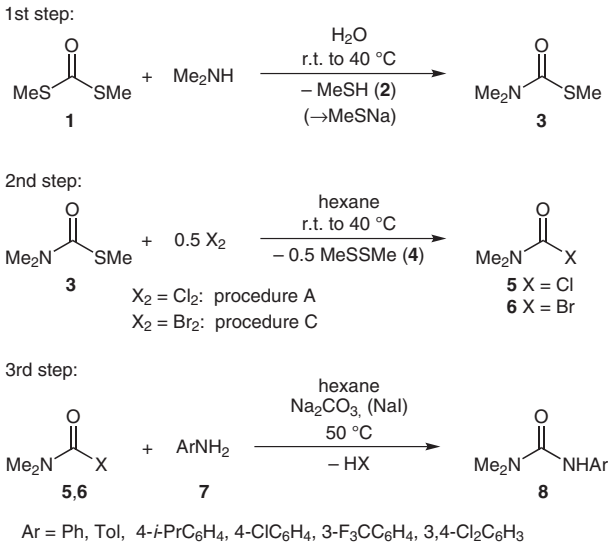
Given the growing demand for environmentally friendly technologies, we present here a new general method for the preparation of *N*,*N*-dimethyl-*N*′-arylureas, which uses *S*,*S*-dimethyl dithiocarbonate as the carbonylating reagent for dimethylamine. The present research has been part of a wide-ranging project that addresses the development of new, safe, and soft synthetic methodologies for the production of intermediates and products, particularly of industrial interest, based on the use of *S*,*S*-dimethyl dithiocarbonate (**1**).

S,*S*-Dimethyl dithiocarbonate (**1**) is a liquid reagent, which is nontoxic and nonhazardous, and is therefore easily handled in full safety. It can easily be prepared in high yield on both laboratory[15] and industrial[16] scale by rearrangement of the corresponding inexpensive *O*,*S*-dimethyl dithiocarbonate. In past research we used *S*,*S*-dimethyl dithiocarbonate as a precursor of methanethiol under phase-transfer-catalysis conditions,[17] and more recently we used it as a phosgene substitute in the carbonylation of primary aliphatic amines for the synthesis of *S*-methyl *N*-alkylthiocarbamates,[18] *N*-alkylureas, *N*,*N*′-dialkylureas, and *N*,*N*,*N*′-trialkylureas,[4] and alkyl and aryl alkylcarbamates.[19]

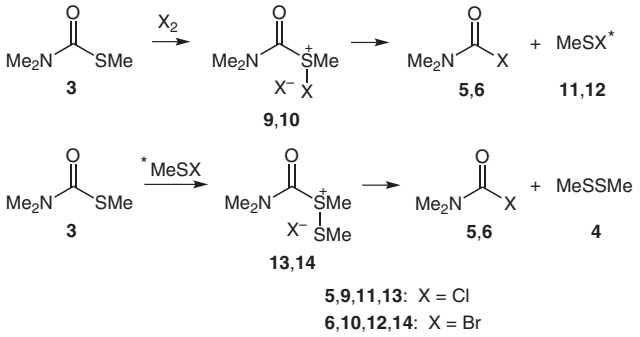
This work demonstrates a new method for the preparation of *N*,*N*-dimethyl-*N*′-arylureas **8**, and consists of three steps, where the second and third steps are carried out in a one-pot fashion (Scheme 1).

In the first step, a 40% aqueous solution of dimethylamine was added slowly, and under stirring, to *S*,*S*-dimethyl dithiocarbonate (**1**), while the temperature of the reaction mixture was maintained at 20–25 °C with an ice bath (Scheme 1). The optimal *S*,*S*-dimethyl dithiocarbonate/dimethylamine molar ratio was 1:1.2. After this addition, the mixture was heated to 40 °C in an oil bath for three

SYNTHESIS 2009, No. 5, pp 0801–0808
Advanced online publication: 27.01.2009
DOI: 10.1055/s-0028-1083340; Art ID: Z22708SS



Scheme 1



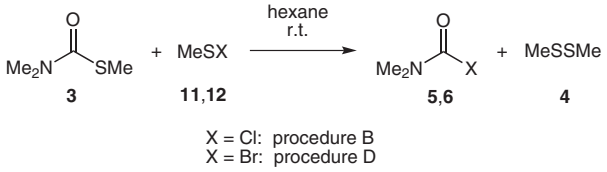
Scheme 2

hours, until completion of the reaction (disappearance of **1**). The newly formed *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**) separated from the reaction mixture as an oily substance; simple extraction with dichloromethane and subsequent evaporation of the solvent under reduced pressure gave the pure product **3** (100% by GC and ^{1}H NMR) in yields higher than 99.5%. During the reaction, one mole of methanethiol (**2**) formed for each mole of *S*,*S*-dimethyl dithiocarbonate (**1**), and was collected in an aqueous solution of sodium hydroxide. When working on large scale, one can recover the methanethiol as sodium methanethiolate in yields higher than 95%.[20]

The second and third steps (Scheme 1) were carried out in anhydrous hexane, in a one-pot fashion; four methods (procedures A–D), differing mainly in the reagent used in the second step for the halogenation of *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**) were used. These will be described in more detail below.

Procedure A: For procedure A, in the second step, the thiocarbamate **3** was reacted with chlorine, in a 1:0.5 molar ratio, to give *N*,*N*-dimethylcarbamoyl chloride (**5**) (Scheme 1). The reaction was carried out at room temperature during the chlorine addition, then at 40 °C for one hour until the disappearance of **3** (by ^{1}H NMR and GC-MS). Only a half mole-equivalent of chlorine was needed to complete the chlorination reaction. In fact, half of **3** was chlorinated by chlorine, while the other half was chlorinated by the methanesulfenyl chloride (**11**) that formed during the reaction (Scheme 2). Indeed, GC-MS and ^{1}H NMR spectroscopy verified the presence of **11** in the reaction mixture.

As indicated in Scheme 2, it may be that *N*,*N*-dimethylcarbamoyl chloride (**5**) is obtained through the formation of the chlorine–thiocarbamate **3** intermediate complexes **9** and **13**; this is consistent with the literature regarding the reactions of halogen (chlorine and bromine) with thiol esters,[21] and with what we recently hypothesized for the reactions of chlorine with *S*-methyl *N*-alkylthiocarbamates.[19b] The mechanism proposed in Scheme 2 is also supported by the presence of dimethyl disulfide (**4**) in the reaction mixtures and by the reaction of **5** with methanesulfenyl chloride (**11**) (Scheme 3).



Scheme 3

In the third step (Scheme 1), the reaction mixture containing *N*,*N*-dimethylcarbamoyl chloride (**5**) was allowed to cool to room temperature (20–25 °C), and sodium carbonate and then sodium iodide (the latter in catalytic amount) were added directly under vigorous stirring. The pH of the mixture reached about 7. The search for the optimal conditions for the third step was done with the use of 3-(trifluoromethyl)aniline (**7**, Ar = 3-$F_3CC_6H_4$) (Table 1, entries 7–10). A solution of the aniline in anhydrous hexane was added slowly to the reaction mixture, always under vigorous stirring. At the end of the addition, the mixture was heated to 50 °C with an oil bath. Under these temperature conditions, *N*,*N*-dimethyl-*N*′-[3-(trifluoromethyl)phenyl]urea (**8e**, fluometuron) formed very slowly, and because of its insolubility in hexane, it separated from the reaction mixture as a colorless solid. Working with a strong excess of *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**) and hence of *N*,*N*-dimethylcarbamoyl chloride (**5**) (Table 1, entries 9 and 10; molar ratio **7/3** = 1:1.75 and 1:2, respectively), the reaction went to completion with the disappearance of the aniline after 16 hours. In contrast, with a smaller excess of **3** (Table 1, entries 7 and 8; molar ratio **7/3** = 1:1.25 and 1:1.5, respectively) the reactions did not go to completion. In fact, it practically stopped after 16 hours, despite reagents **3** and **7** still being present.

Product **8e** was then separated as follows: the solid substances, i.e. sodium carbonate and **8e**, were collected by filtration on a Buchner funnel and washed with hexane, directly on the Buchner funnel, to eliminate any unchanged aniline and other impurities {tetramethylurea and

Table 1 Preparation of *N*,*N*-Dimethyl-*N*′-arylureas **8a–f**

Entry	Ar	Reagent	Procedure	Ratio **7/3**	Time (h)	**8**	Yield (%)[a] (purity, %)[b]	Mp (°C) Crude	Recryst.[c]	Lit.
1	Ph	Cl_2	A	1:1.25	16	**8a**	97 (99.5)	133	133.8–134.0	131–133[24] 134.1[25]
2		Br_2	C	1:1.5	5	**8a**	95 (100)	133.2–133.8		
3	Tol	Cl_2	A	1:1.25	16	**8b**	98 (100)	155.0–155.5	155.5–155.7	153–155[26]
4	4-*i*-PrC_6H_4	Cl_2	A	1:1.25	16	**8c**	98 (99.8)	156	157.8–158.4	155–156[24]
5	4-ClC_6H_4	Cl_2	A	1:1.25	16	**8d**	88 (100)	174.8	175	170.5–171.5[24] 174.5[25]
6			A	1:1.5	16	**8d**	93 (100)	174.8		
7	3-F_3C-C_6H_3	Cl_2	A	1:1.25	16	**8e**	88 (99.8)	162.9–163.4	163.4–164.4	163.0–164.5[24] 160.3[25]
8		Cl_2	A	1:1.5	16	**8e**	91 (99.8)	162.9–163.4		
9		Cl_2	A	1:1.75	16	**8e**	95 (99.7)	162.7–163.3		
10		Cl_2	A	1:2	16	**8e**	98 (99.7)	162.9–163.3		
11		MeSCl	B	1:2	16	**8e**	98 (99.8)	162.9–163.6		
12		Br_2	C	1:1.5	6	**8e**	85 (99.7)	162.0–163.7		
13		Br_2	C	1:2	6	**8e**	91 (99.7)	161.9–163.1		
14		MeSBr	D	1:2	6	**8e**	92 (99.6)	160.2–161.2		
15	3,4-$Cl_2C_6H_3$	Cl_2	A	1:1.5	24	**8f**	87 (99.5)	157	158.7	153.5–155[24] 157.5[25]
16		Cl_2	A	1:2	24	**8f**	93 (99.5)	156.8–157		

[a] Yields of the isolated crude products.
[b] Purity determined by GC.
[c] Recrystallized from EtOH.

traces of 1,1,5,5-tetramethyl-3-[3-(trifluoromethyl)phenyl]biuret (**15**)}. Subsequent dichloromethane–water treatment led to the removal of the sodium carbonate. After drying of the solution over sodium sulfate, and evaporation of the solvent under reduced pressure, fluometuron (**8e**) was obtained in the following yields (and purity): 88% (99.8%), 91% (99.8%), 95% (99.7%), 98 (99.7%) (Table 1, entries 7, 8, 9, and 10, respectively). In the cases of the reactions shown in Table 1, entries 7 and 8, the unchanged 3-(trifluoromethyl)aniline could be recovered almost quantitatively. Also to be noted is that, when working on large scale, dimethyl disulfide (**4**), which in the second step was formed in the amount of a half mole for each mole of **3**, could be recovered in greater than 90% yield by fractional distillation of the hexane solutions.[20]

With regard to this third step, the following points are noteworthy: (i) The reaction of 3-(trifluoromethyl)aniline with *N*,*N*-dimethylcarbamoyl chloride (**5**) must be carried out at a maximum temperature of 50 °C. In fact, higher temperatures result in increased amounts of the byproduct 1,1,5,5-tetramethyl-3-[3-(trifluoromethyl)phenyl]biuret (**15**) (Figure 1), which is produced by the reaction of excess **5** with the already formed fluometuron (**8e**) (see experimental procedures). (ii) Catalytic amounts of sodium iodide shorten the reaction time and lead to higher yields of the target products **8**. Indeed, trial reactions carried out in the absence of sodium iodide provided fluometuron (**8e**) in yields of only 41 and 54% after 24 and 48 hours, respectively. Procedure A was also used for the synthesis of *N*,*N*-dimethyl-*N*′-arylureas **8a–d** and **8f** (Table 1, entries 1, 3–6, 15, and 16). Under the better conditions, the yields were greater than 93% and the purity exceeded 99.5%.

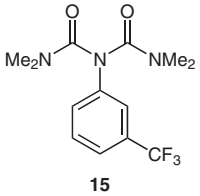


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Figure 1

Procedure B: In the second step of procedure B (see Scheme 3), the chlorination of *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**) was carried out in anhydrous hexane with methanesulfenyl chloride (**11**) (prepared in situ by reaction of chlorine with dimethyl disulfide),[22] in a molar ratio of 1 to 1.5. The reaction was complete in one hour at room temperature and provided *N*,*N*-dimethylcarbamoyl chloride (**5**) and dimethyl disulfide (**4**) (Scheme 3). The third step (see Scheme 1), i.e. the reaction of **5** with 3-(trifluoromethyl)aniline, was carried out at 50 °C under procedure A conditions, with a **7/3** molar ratio of 1:2. It went to completion in 16 hours and gave pure fluometuron (**8e**) in 98% yield (Table 1, entry 11).

Procedure C: In the second step of procedure C (see Scheme 1), the halogenation of *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**) was carried out in anhydrous hexane with bromine, molar ratio 1:0.7, giving *N*,*N*-dimethylcarbamoyl bromide (**6**) and dimethyl disulfide (**4**). The reaction went to completion in one hour at room temperature. As in the case of chlorination with chlorine, **3** was brominated by both bromine and by the methanesulfenyl bromide (**12**) formed during the reaction (Scheme 2). Indeed, the presence of **12** in the reaction mixture was evidenced by ^{1}H NMR spectroscopy. Also in this case, it may be that *N*,*N*-dimethylcarbamoyl bromide (**6**) is obtained via bromine–thiocarbamate **3** intermediate complexes **10** and **14** (Scheme 2). The third step, and therefore the subsequent reaction of **6** with 3-(trifluoromethyl)aniline (Scheme 1), was carried out at 50 °C in the presence of sodium carbonate, at pH 5–6. The conditions were those described for procedure A. The only difference was that *N*,*N*-dimethylcarbamoyl bromide (**6**) proved much more reactive than the corresponding chloride (**5**). In fact, when the reaction was carried out in the absence of sodium iodide and with a **7/3** molar ratio of 1:2 (Table 1, entry 13), it went to completion after only six hours, providing pure fluometuron (**8e**) in high yield (91%). Moreover, a trial reaction, carried out under the same conditions but in the presence of sodium iodide (in catalytic amounts), revealed the ineffectiveness of the catalyst in the reactions where the reagent was carbamoyl bromide. In fact, both reaction time and yield were comparable to those of Table 1, entry 13. With a smaller excess of carbamoyl bromide (**6**), i.e. a **7/3** molar ratio of 1:1.5 (Table 1, entry 12), the reaction stopped after six hours, despite the presence of both reagents. The **8e** yield was 85% and the unchanged 3-(trifluoromethyl)aniline was recovered almost quantitatively. Procedure C was also used for the synthesis of *N*,*N*-dimethyl-*N*′-phenylurea (**8a**), which was obtained in 95% yield (Table 1, entry 2).

Procedure D: In the second step of procedure D (see Scheme 3), *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**) was reacted with methanesulfenyl bromide (**12**) (prepared in situ by reaction of bromine with dimethyl disulfide),[23] in a 1:1.5 molar ratio. The reaction, carried out in anhydrous hexane at room temperature, went to completion in one hour and gave *N*,*N*-dimethylcarbamoyl bromide (**6**) and dimethyl disulfide (**4**). In the third step (see Scheme 1), the subsequent reaction of **6** with 3-(trifluoromethyl)aniline was carried out under the conditions of procedure C. When a **7/3** molar ratio of 1:2 was used (Table 1, entry 14), the reaction was complete in six hours, giving pure fluometuron (**8e**) in 92% yield.

It is also important to emphasize that various attempts to directly react *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**) with 3-(trifluoromethyl)aniline to obtain fluometuron (**8e**) were unsuccessful (see experimental section).

In conclusion, this research has established a general, simple, and effective three-step method for the preparation of *N*,*N*-dimethyl-*N*′-arylureas **8**, using *S*,*S*-dimethyl dithiocarbonate (**1**) as the starting reagent. The results described here demonstrate the synthetic value of *S*,*S*-dimethyl dithiocarbonate, which is a liquid, nontoxic, and no-risk reagent, as an efficient phosgene substitute in carbonylation reactions for the preparation of various products, particularly also of industrial interest. The target products **8a–f** were obtained almost pure in 85–98% yield. The average yield of the 16 considered reactions was 93%, based on the anilines. Several of the products prepared [fenuron (**8a**), isoproturon (**8c**), monuron (**8d**), fluometuron (**8e**), and diuron (**8f**)] are currently marketed as herbicides. The reactions also produced byproducts of industrial interest, namely methanethiol (**2**) and dimethyl disulfide (**4**), in amounts of one mole and half a mole, respectively, for each mole of *S*,*S*-dimethyl dithiocarbonate. In large-scale preparations,[20] these could be recovered in high yield, with obvious economic advantages. Therefore, given the simplicity, economic benefits, high yields, and high purity of the ureas **8**, the new method is well suited for use on both laboratory and industrial scales.

All the reactions were performed in oven-dried glassware with anhyd hexane as solvent. No particular device was, however, adopted to exclude moisture or oxygen. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra of samples in $CDCl_3$ were recorded on a Bruker Avance 200 spectrometer. Mass spectra were recorded on an AT 5973N mass-selective detector connected to an AT 6890N GC, cross-linked methylsilicone capillary column. Details for the reactions and yields for the pure (GC, GC-MS, ^{1}H NMR) *N*,*N*-dimethyl-*N*′-arylureas **8a–f** are listed in Table 1. The molecular structure of all the products were confirmed by comparison of their physical (mp or bp) and spectral data (MS, ^{1}H NMR) with those reported in the literature. All the amines were purchased from the Aldrich Chemical Co. and used without further purification. *S*,*S*-Dimethyl dithiocarbonate was supplied by Oxon Italia S.p.A. (Italy)[16] or prepared as described in the literature.[15]

_S_-Methyl _N_,_N_-Dimethylthiocarbamate (3)

A 40% aq soln of Me_2NH (13.50 g, 0.12 mol) was added dropwise over 15–20 min to **1** (12.20 g, 0.10 mol) under stirring. The reaction was mildly exothermic, and during the addition the temperature of the mixture was maintained at 20–25 °C with an ice–water bath. The progress of the reaction was monitored by GC and GC-MS analyses. After the addition, the reaction mixture was heated to 40 °C with an oil bath and maintained at that temperature under stirring for 3 h, until disappearance of starting material **1**. The only product formed was **3**. The mixture was diluted with CH_2Cl_2 (200 mL) and the organic layer was washed with a small amount of H_2O (10–15 mL), dried (Na_2SO_4), and evaporated under reduced pres-

sure. The crude residue was **3**. [The methanethiol (**2**) that formed during the reaction was collected in a 10–15% aq soln of NaOH. When working on large scale,[20] it could be recovered as sodium methanethiolate in yields >95%.]

Yield: 11.84 g (99.5%); 100% purity (GC); bp 64–65 °C/45 Torr (Lit.[27] 54 °C/6 Torr).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 2.98 (s, 6 H, 2 × CH_3). Identical to that reported.[27]

MS (EI, 70 eV): *m*/*z* (%) = 119 (40) [M$^+$], 72 (100), 42 (11).

N,*N*-Dimethyl-*N*′-[3-(trifluoromethyl)phenyl]urea (8e, Fluometuron) by Procedure A; Typical Procedure

Optimal method shown in Table 1, entry 10: The crude **3** (2.38 g, 20 mmol) was dissolved in anhyd hexane (10 mL) and the soln was stirred at r.t. Cl_2 gas (0.71 g, 10 mmol) was slowly bubbled through the soln for 30–40 min. The reaction was mildly exothermic and the mixture turned deep yellow. After the addition of the Cl_2, GC-MS and ^{1}H NMR analyses showed the presence of MeSCl {**11**; *m*/*z* = 82 [M$^+$]; δ = 2.82 (s, CH_3); identical to that reported[28]}, dimethyl disulfide {**4**; *m*/*z* = 94 [M$^+$]; δ = 2.42 (s, 2 × CH_3)}, *N*,*N*-dimethylcarbamoyl chloride {**5**; *m*/*z* = 107 (37) [M$^+$], 78 (5), 72 (100), 63 (8), 56 (10), 43 (5), 42 (18); δ = 3.02 (s, 3 H, CH_3), 3.12 (s, 3 H, CH_3); identical to those of an authentic sample of analytical purity (Aldrich)}, as the major product, together with the starting thiocarbamate **3** {*m*/*z* = 119 [M$^+$]}. To complete the chlorination reaction, the mixture was heated to 40 °C with an oil bath. Under these conditions, the color of the mixture gradually faded and became pale yellow. After 1 h, GC analysis showed the complete disappearance of thiocarbamate **3** and the presence of dimethyl disulfide (**4**) and *N*,*N*-dimethylcarbamoyl chloride (**5**) as only products.

The reaction mixture was allowed to cool to r.t. and diluted with anhyd hexane (10 mL). Then anhyd Na_2CO_3 (2.12 g, 20 mmol) and anhyd NaI (0.06 g, 0.4 mmol) were added in one portion, under vigorous stirring. The pH of the soln above the carbonate was ca. 7 (when the pH was lower, another portion of Na_2CO_3 was added until the pH became ca. 7). A soln of 3-(trifluoromethyl)aniline (**7**, Ar = 3-$F_3CC_6H_4$; 1.61 g, 10 mmol) in anhyd hexane (5 mL) was added dropwise over 5–10 min, and the reaction mixture was heated to 50 °C with an oil bath, while vigorous stirring was maintained. The target product **8e** formed slowly, and because of its insolubility in hexane, it separated from the reaction mixture as a colorless solid, immediately after being formed. The progress of the reaction was monitored by GC analysis of the hexane soln, that evidenced the progressive slow decrease in the amounts of the two reagents, i.e. *N*,*N*-dimethylcarbamoyl chloride (**5**) and 3-(trifluoromethyl)aniline. After 16 h the reaction was complete [disappearance of 3-(trifluoromethyl)aniline]. After the mixture had cooled to r.t., anhyd hexane (20 mL) was added, under stirring. The solid substances (Na_2CO_3 and **8e**) were collected by filtration on a Buchner funnel, washed with hexane (3 × 15 mL) directly on the Buchner funnel, and then treated with CH_2Cl_2–H_2O (1:1, 200 mL). The aq soln was separated and extracted again with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with H_2O (2 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure to afford crude **8e**.

(*Notes*: (a) GC-MS analysis of the collected hexane solns showed the presence of dimethyl disulfide (**4**) and several byproducts. Between these, tetramethylurea {*m*/*z* = 116 [M$^+$]} and traces of 1,1,5,5-tetramethyl-3-[3-(trifluoromethyl)phenyl]biuret {**15**; *m*/*z* = 303 [M$^+$]} were revealed. When working on a large scale,[20] dimethyl disulfide (**4**) could be recovered in yields >90% by fractional distillation of the organic soln, which had been dried previously (Na_2SO_4). (b) When the reaction was carried out in the absence of NaI, it was slower and the yield of **8e** was only 41% (0.95 g) and 54% (1.25 g), respectively, after 24 and 48 h.)

Yield: 2.27 g (98%, based on **7**); 99.8% purity (GC); mp 162.9–163.8 °C (crude), 163.4–164.4 °C (recrystallized from EtOH) (Lit.[24] 163–164.5 °C; Lit.[25] 160.3 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.01 (s, 6 H, 2 × CH_3), 6.74 (br s, 1 H, NH), 7.24 (app d, *J* = 7.9 Hz, 1 H, ArH), 7.45 (app t, *J* = 7.9 Hz, 1 H, ArH), 7.56 (app d, *J* = 7.9 Hz, 1 H, ArH), 7.54 (s, 1 H, ArH). Similar to that reported.[25,29]

MS (EI, 70 eV): *m*/*z* (%) = 232 (37) [M$^+$], 187 (6), 72 (100), 44 (7).

Alternative method shown in Table 1, entry 7: The reaction was carried out according to procedure A as described above, but a different molar ratio of the reagents was used: **3** (1.49 g, 12.5 mmol), Cl_2 gas (0.44 g, 6.25 mmol), **7** (Ar = 3-$F_3CC_6H_4$; 1.61 g, 10 mmol), anhyd Na_2CO_3 (1.33 g, 12.5 mmol), and anhyd NaI (0.04 g, 0.25 mmol). In this case, the reaction did not reach completion. In fact, after 16 h at 50 °C, the reaction practically stopped although both reagents **3** and **7** were still present. The above workup afforded fluometuron (**8e**); yield: 2.04 g (88%, based on **7**); 99.8% purity (GC); mp 162.9–163.4 °C. The collected hexane solns were treated with 10% aq HCl (50 mL). The aq acid soln was basified with 30% aq NaOH and extracted with CH_2Cl_2 (2 × 50 mL). The organic solns were collected, washed repeatedly with H_2O (3 × 50 mL) to eliminate the byproduct tetramethylurea, dried (Na_2SO_4), and evaporated under reduced pressure to recover the unchanged 3-(trifluoromethyl)aniline; yield: 0.18 g (11%).

Alternative methods shown in Table 1, entries 8 and 9: The reactions were carried out according to procedure A as described above, but the reagent molar ratio **3**/**7** was 1.5:1 and 1.75:1, respectively. The second reaction was complete after 16 h at 50 °C and afforded **8e**; yield: 2.20 g (95%); 99.7% purity (GC). In contrast, the first reaction practically stopped, although the reagents were still present; yield (**8e**): 2.11 g (91%); 99.8% purity (GC); unchanged 3-(trifluoromethyl)aniline was recovered (0.14 g, 9%).

N,*N*-Dimethyl-*N*′-[3-(trifluoromethyl)phenyl]urea (8e, Fluometuron) by Procedure B (Table 1, entry 11)

According to a literature procedure,[22] Cl_2 gas (0.53 g, 7.5 mmol) was slowly bubbled through a soln of dimethyl disulfide (0.71 g, 7.5 mmol) in anhyd hexane (10 mL) for ca. 20 min, under slight stirring and maintenance of the reaction mixture temperature at –10 to 0 °C with an ice bath. After the addition, ^{1}H NMR analysis of the orange soln thus obtained showed the disappearance of dimethyl disulfide and the presence of MeSCl [**11**; δ = 2.82 (s, CH_3); identical to that reported[28]], as the only product. A soln of the crude **3** (1.19 g, 10 mmol) in anhyd hexane (5 mL) was added dropwise at r.t., while slight stirring was maintained. Then the mixture was allowed to warm to r.t. After 1 h the color of the mixture faded and became pale yellow. ^{1}H NMR analysis showed the disappearance of **3** and the formation of **5** [δ = 3.02 (s, 3 H, CH_3), 3.12 (s, 3 H, CH_3)] and dimethyl disulfide [**4**; δ = 2.42 (s, 2 × CH_3)].

The reaction mixture was diluted with anhyd hexane (10 mL), and anhyd Na_2CO_3 (1.59 g, 15 mmol) and anhyd NaI (0.06 g, 0.4 mmol) were added in one portion, under vigorous stirring. The pH of the soln above the carbonate was ca. 7. A soln of **7** (Ar = 3-$F_3CC_6H_4$; 0.81 g, 5 mmol) in anhyd hexane (5 mL) was added dropwise over 5–10 min. Then the reaction mixture was heated to 50 °C with an oil bath, while vigorous stirring was maintained. The target product **8e** formed slowly, and it separated from the reaction mixture as a colorless solid, immediately after being formed. The reaction was complete (disappearance of **7**) after 16 h. The workup described in procedure A (Table 1, entry 10) afforded fluometuron (**8e**).

Yield: 1.14 g (98%; based on **7**); 99.8% purity (GC); mp 162.9–163.6 °C.

N,*N*-Dimethyl-*N*′-[3-(trifluoromethyl)phenyl]urea (8e, Fluometuron) by Procedure C

Optimal method shown in Table 1, entry 13: The reaction was carried out in a reactor that was protected from light. A soln of Br_2 (2.24 g, 14 mmol) in anhyd hexane (5 mL) was added dropwise over 5 min into a soln of the crude **3** (2.38 g, 20 mmol) in the same solvent (15 mL), at r.t. and under slight stirring. A brown-red soln was obtained. The progress of the reaction was monitored by GC-MS and ^{1}H NMR analyses. These showed the presence of dimethyl disulfide {**4**; *m*/*z* = 94 [M$^+$]; δ = 2.42 (s, CH_3)}, *N*,*N*-dimethylcarbamoyl bromide {**6**; *m*/*z* = 151 (4) [M$^+$], 72 (100), 56 (10), 43 (5), 42 (15); δ = 3.09 (s, 3 H, CH_3), 3.16 (s, 3 H, CH_3)[30,31]}, and the starting thiocarbamate **3** {*m*/*z* = 119 [M$^+$]}. ^{1}H NMR analysis revealed also the presence of MeSBr [**12**; δ = 2.92 (s, CH_3); NMR data not reported in the literature]. After 1 h the reaction was complete and dimethyl disulfide (**4**) and *N*,*N*-dimethylcarbamoyl bromide (**6**) were the only products.

The reaction mixture was diluted with anhyd hexane (10 mL). Then anhyd Na_2CO_3 (6.36 g, 60 mmol) was added under vigorous stirring. The color of the mixture became pale yellow and the pH of the soln above the carbonate became 5–6. A soln of 3-(trifluoromethyl)aniline (**7**, Ar = 3-$F_3CC_6H_4$; 1.61 g, 10 mmol) in anhyd hexane (5 mL) was added dropwise over 5–10 min, and the mixture was heated to 50 °C with an oil bath, under vigorous stirring. During the reaction the target product **8e** formed fast and separated from the reaction mixture as a colorless solid, immediately after being formed. The progress of the reaction was monitored by GC analysis of the hexane soln that evidenced the progressive decrease in the amounts of the two reagents **6** and **7**. The reaction was complete after 6 h (disappearance of **7**). The workup described in procedure A (Table 1, entry 10) afforded fluometuron (**8e**).

Yield: 2.11 g (91%; based on **7**); 99.7% purity (GC); mp 161.9–163.1 °C.

[When the reaction was carried out in the presence of NaI (0.06 g, 0.4 mmol), it was completed in the same time (6 h) and afforded pure fluometuron (**8e**) in the same yield (2.11 g, 91%).]

Alternative method shown in Table 1, entry 12: The reaction was carried out according to procedure C described above, but a different molar ratio of reagents was used: **3** (1.79 g, 15 mmol), Br_2 (1.68 g, 10.5 mmol), **7** (Ar = 3-$F_3CC_6H_4$; 1.61 g, 10 mmol), and anhyd Na_2CO_3 (4.77 g, 45 mmol). In this case, the reaction did not reach completion. In fact, after 6–7 h at 50 °C, the reaction practically stopped although both reagents were still present. The above workup (Table 1, entry 7) afforded fluometuron (**8e**); unchanged 3-(trifluoromethyl)aniline was also recovered (0.16 g, 10%).

Yield: 1.97 g (85%, based on **7**); 99.7% purity (GC); mp 162.0–163.7 °C.

N,*N*-Dimethyl-*N*′-[3-(trifluoromethyl)phenyl]urea (8e, Fluometuron) by Procedure D (Table 1, entry 14)

The reaction was carried out in a reactor that was protected from light. According to a literature procedure,[23] a soln of Br_2 (1.20 g, 7.5 mmol) in anhyd hexane (5 mL) was added dropwise over 5–10 min to a soln of dimethyl disulfide (0.71 g, 7.5 mmol) in the same solvent (5 mL), at r.t. and under slight stirring. After 1 h, ^{1}H NMR analysis of the deep red soln showed the disappearance of dimethyl disulfide and the presence of MeSBr [**6**; δ = 2.92 (s, CH_3)] as the only product. A soln of the crude **3** (1.19 g, 10 mmol) in anhyd hexane (5 mL) was added dropwise at r.t., while slight stirring was maintained. After 2 h, ^{1}H NMR analysis of the reaction mixture showed the disappearance of **3** and the formation of *N*,*N*-dimethylcarbamoyl bromide [**6**; δ = 3.09 (s, 3 H, CH_3), 3.16 (s, 3 H, CH_3)] and dimethyl disulfide [**4**; δ = 2.42 (s, 2 × CH_3)].

Anhyd Na_2CO_3 (3.18 g, 30 mmol) was added under vigorous stirring. The color of the mixture became pale yellow and the pH of the soln above the carbonate became 5–6. A soln of **7** (Ar = 3-$F_3CC_6H_4$; 0.81 g, 5 mmol) in anhyd hexane (5 mL) was added dropwise over 5–10 min, and the mixture was heated to 50 °C with an oil bath, while vigorous stirring was maintained. The title compound **8e** formed fast and separated from the reaction mixture as a colorless solid, immediately after being formed. The reaction was complete after 6 h. The workup described in procedure A (Table 1, entry 10) afforded fluometuron (**8e**).

Yield: 1.07 g (92%, based on **7**); 99.6% purity (GC); mp 160.2–161.2 °C.

N,*N*-Dimethyl-*N*′-arylureas 8a–f

N,*N*-Dimethyl-*N*′-arylureas **8a**–**d** and **8f** were also prepared according to procedure A; *N*,*N*-dimethyl-*N*′-(phenyl)urea (**8a**) was also prepared according to procedure C. Yields and physical data of the virtually pure (GC, ^{1}H NMR) crude compounds are listed in Table 1; spectral data are given below.

N,*N*-Dimethyl-*N*′-phenylurea (8a, Fenuron)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.99 (s, 6 H, 2 × CH_3), 6.51 (br s, 1 H, NH), 7.01 (app t, *J* = 7.2 Hz, 1 H, ArH), 7.26 (app t, *J* = 7.6 Hz, 2 H, 2 × ArH), 7.38 (app d, *J* = 7.6 Hz, 2 H, 2 × ArH). Similar to that reported.[25,29,32]

MS (EI, 70 eV): *m*/*z* (%) = 164 (57) [M$^+$], 119 (11), 91 (5), 72 (100), 65 (7).

N,*N*-Dimethyl-*N*′-(4-tolyl)urea (8b)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 3.00 (s, 6 H, 2 × CH_3), 6.28 (br s, 1 H, NH), 7.07 (d, *J* = 8.4 Hz, 2 H, 2 × ArH), 7.24 (d, *J* = 8.4 Hz, 2 H, 2 × ArH). Similar to that reported.[29]

MS (EI, 70 eV): *m*/*z* (%) = 178 (55) [M$^+$], 133 (13), 132 (7), 120 (5), 106 (6), 104 (5), 77 (9), 72 (100), 45 (7).

N-(4-Isopropylphenyl)-*N*′,*N*′-dimethylurea (8c, Isoproturon)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.6 Hz, 6 H, 2 × CH_3), 2.79–2.92 (m, 1 H, CH), 3.01 (s, 6 H, 2 × CH_3), 6.40 (br s, 1 H, NH), 7.14 (d, *J* = 8.8 Hz, 2 H, 2 × ArH), 7.28 (d, *J* = 8.8 Hz, 2 H, 2 × ArH). Similar to that reported.[32]

MS (EI, 70 eV): *m*/*z* (%) = 206 (61) [M$^+$], 192 (5), 191 (35), 161 (7), 147 (6), 146 (53), 128 (8), 91 (10), 72 (100), 45 (6).

N-(4-Chlorophenyl)-*N*′,*N*′-dimethylurea (8d, Monuron)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.00 (s, 6 H, 2 × CH_3), 6.40 (br s, 1 H, NH), 7.21 (d, *J* = 8.8 Hz, 2 H, 2 × ArH), 7.31 (d, *J* = 8.8 Hz, 2 H, 2 × ArH). Similar to that reported.[25,32]

MS (EI, 70 eV): *m*/*z* (%) = 198 (30) [M$^+$], 153 (9), 73 (6), 72 (100).

N-(3,4-Dichlorophenyl)-*N*′,*N*′-dimethylurea (8f, Diuron)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.00 (s, 6 H, 2 × CH_3), 6.42 (br s, 1 H, NH), 7.19–7.21 (m, 1 H, ArH), 7.22–7.30 (m, 1 H, ArH), 7.59 (app s, 1 H, ArH). Similar to that reported.[25,32]

MS (EI, 70 eV): *m*/*z* (%) = 232 (17) [M$^+$], 189 (11), 187 (18), 124 (10), 73 (6), 72 (100), 44 (7).

Trial Reactions

Attempts To Prepare Fluometuron (8e) by Direct Reaction of *S*-Methyl *N*,*N*-Dimethylthiocarbamate (3) with 3-(Trifluoromethyl)aniline

1. A mixture of *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**; 0.60 g, 5 mmol) and 3-(trifluoromethyl)aniline (**7**, Ar = 3-$F_3CC_6H_4$; 1.13 g, 7 mmol) was heated at 120–125 °C with an oil bath, under stirring. After 24 h, GC and ^{1}H NMR analyses showed that the two reagents were unchanged and no trace of **8e** was present.

2. A soln of *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**; 0.60 g, 5 mmol) and 3-(trifluoromethyl)aniline (**7**, Ar = 3-$F_3CC_6H_4$; 1.13 g, 7

mmol) in anhyd toluene (5 mL) was heated at reflux (110 °C) with an oil bath, under stirring. After 24 h, GC and ^{1}H NMR analyses showed that the two reagents were unchanged and no trace of **8e** was present.

Reaction between *N*,*N*-Dimethylcarbamoyl Chloride (5) and 3-(Trifluoromethyl)aniline (7, Ar = 3-$F_3CC_6H_4$) in Anhydrous Hexane under Reflux or at 60 or 65 °C

1. As described above, *N*,*N*-dimethylcarbamoyl chloride (**5**) was prepared starting from *S*-methyl *N*,*N*-dimethylthiocarbamate (**3**; 2.38 g, 20 mmol) and Cl_2 (0.71 g, 10 mmol) in anhyd hexane (10 mL). According to procedure A, **5** was then reacted with 3-(trifluoromethyl)aniline (**7**, Ar = 3-$F_3CC_6H_4$; 1.61 g, 10 mmol), in the presence of Na_2CO_3 (2.12 g, 20 mmol) and NaI (0.06 g, 0.4 mmol). The mixture was heated to reflux (69 °C) with an oil bath and the progress of the reaction was monitored by GC, GC-MS, and ^{1}H NMR analyses. Fluometuron (**8e**) and 1,1,5,5-tetramethyl-3-[3-(trifluoromethyl)phenyl]biuret (**15**) began to form slowly and both separated from the reaction mixture as colorless solids, immediately after being formed (GC, GC-MS, and ^{1}H NMR analyses). Only traces of compound **15** dissolved in the solvent. After 16 h, 3-(trifluoromethyl)aniline (**7**, Ar = 3-$F_3CC_6H_4$) disappeared while part of the starting *N*,*N*-dimethylcarbamoyl chloride (**5**) was still present in the hexane soln. The mixture was worked up as described in procedure A. The crude residue consisted of only two products, **8e** and **15**, which were separated by column chromatography (silica gel, CH_2Cl_2–EtOAc, 4:1). This gave pure fluometuron (**8e**) and pure 1,1,5,5-tetramethyl-3-[3-(trifluoromethyl)phenyl]biuret (**15**). (GC-MS analysis of the collected hexane solns showed the presence of **5**, dimethyl disulfide {**4**; *m*/*z* = 94 [M$^+$]}, tetramethylurea {*m*/*z* = 116 [M$^+$]}, **15** (traces), and other byproducts.)

Yield (**8e**): 1.72 g (74%, based on **7**); mp 161.5–162.6 °C.

Yield (**15**): 0.39 g (13%, based on **7**); mp 144.1–145.5 °C; 147.7–148.6 °C (recrystallized from EtOH) (Lit.[33] 140 °C); spectral data not reported before.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.90 (s, 6 H, 2 × CH_3), 7.16–7.26 (m, 1 H, ArH), 7.26–7.31 (m, 1 H, ArH), 7.42–7.51 (m, 2 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.8 (CH_3), 123.1, 123.2 (CH), 123.9, 124.0 (CH), 117.0, 122.4, 127.8, 133.2 (q, J_{C-F} = 272 Hz, CF_3), 129.6 (CH), 131.4 (CH), 132.3, 132.9, 133.6, 134.2 (q, J_{C-F} = 32.8 Hz, *C*-CF_3), 143.0 (C-N), 158.7 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 303 (15) [M$^+$], 188 (10), 72 (100).

2. After the disappearance of 3-(trifluoromethyl)aniline (**7**, Ar = 3-$F_3CC_6H_4$), the above reaction mixture was refluxed for another 8 h, until *N*,*N*-dimethylcarbamoyl chloride (**5**) had also disappeared. The above workup afforded pure **8e** and pure **15**.

Yield (**8e**): 1.19 g (51%); mp 162.3–163.6 °C; yield (**15**): 1.15 g (38%); mp 145.1–146.7 °C.

3. The reaction was carried out as described above (trial reaction 2) with the only difference that the mixture was heated at 60 °C, instead of at reflux. Also in this case, 3-(trifluoromethyl)aniline (**7**, Ar = 3-$F_3CC_6H_4$) disappeared after 16 h. The above workup afforded pure **8e** and pure **15**.

Yield (**8e**): 2.19 g (94%); mp 162.7–163.9 °C; yield (**15**): 0.15 g (5%); mp 144–145 °C.

4. The same reaction, carried out at 65 °C for 16 h, afforded pure **8e** and pure **15**.

Yield (**8e**): 1.58 g (68%); mp 163.6–163.8 °C; yield (**15**): 0.45 g (15%); mp 146–147 °C.

Acknowledgment

This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the National Research Council (CNR), Italy, National Project 'New synthetic methodologies for industrial intermediates and products' and by the University of Turin.

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