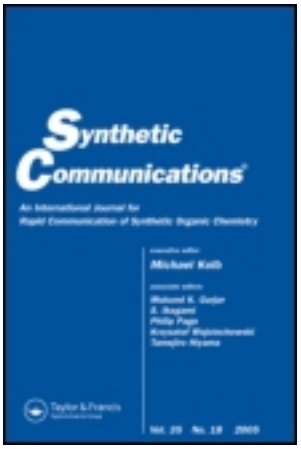

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IMPROVED METHOD FOR THE PREPARATION OF 1,1-DIMETHYL-3-ARYLUREAS USING CHLOROCARBONYLSULFENYL CHLORIDE

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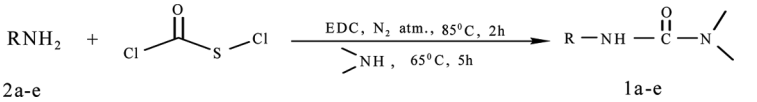
GRAPHICAL ABSTRACT



Abstract *A convenient procedure for preparing some arylureas having herbicidal properties is reported. The method has two steps: (1) reaction of arylamine with chlorocarbonylsulfenyl chloride in the presence of nonpolar solvent to produce aryl carbonylsulfenyl chloride and (2) reaction with dimethylamine in a two-phase reaction catalysed by phase-transfer catalyst to produce the corresponding aryl ureas.*

Keywords Arylureas; carbonylation; chlorocarbonylsulfenyl chloride; isoproturon; p-cumidine

INTRODUCTION

A series of dimethylamine substituted aryl urea derivatives (**1**) are well-known commercial herbicides. Some of these herbicides shown in Fig. 1 [e.g., isoproturon (**1a**), fenuron (**1b**), monuron (**1c**), diuron (**1d**), and metoxuron (**1e**)] have been produced on an industrially large scale.

Several methods for the synthesis of aryl urea derivatives (**1a–e**) have been reported in the literature. Initially in the early fifties,[1] these were developed as industrial herbicides, and several are still on the market. Subsequently, these were also used in the other agricultural applications.[2–7] There is a considerable amount of literature available, especially patents, dealing with a wide variety of procedures for the preparation of arylurea derivatives, and the majority of the procedures can be classified into five groups: (a) phosgenation of primary arylamines with the formation of the corresponding aryl isocyanates and their subsequent reaction in situ

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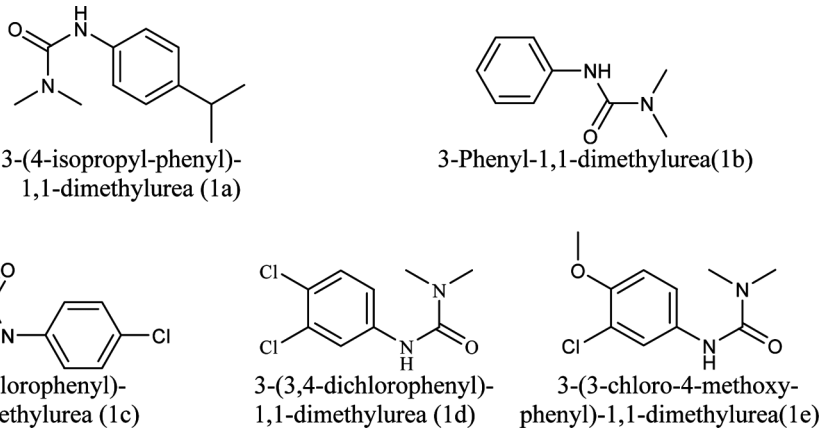


Figure 1. Some commercially available herbicides.

with anhydrous dimethylamine,[8,9] (b) reactions of aryl isocynates with anhydrous dimethylamine,[10–14] aqueous dimethylamine[15–17] or dimcarb,[18] (c) reactions of primary arylamines with dimethylcarbamoyl chloride,[19–24] (d) transamidation of urea with primary arylamines and subsequent transamidation of the resultant products with dimeth ylamine,[25,26] transamidation of diarylureas with dimethylamines,[27–30] and the transamidation of dimethylurea with primary arylamines,[27] and (e) oxidative–reductive carbonylation of nitriarenes and dimethylamine with carbon monoxide as catalyst.[17,31,33]

The present study aims to elaborate a novel economically and commercially viable method for the preparation of dimethylamine substituted aryl urea derivatives having the general formula **1**. In the present communication, the arylamines are first reacted with chlorocarbonylsulfenyl chloride in ethylene dichloride under a nitrogen atmosphere. The resulting aryl carbonylsulfenyl chlorides react with dimethylamine in a two-phase reaction using a phase-transfer catalyst to produce corresponding arylureas.

RESULTS AND DISCUSSION

In the present work, carbonylation of p-cumidine with chlorocarbonylsulfenyl chloride (1:1.04 M) at ~85 °C over 2 h under N_2 atm. was followed by condensation with aqueous solution of dimethylamine in two phase reaction using different solvents and different phase-transfer catalysts at ~65 °C over 5 h (Table 1). The maximum yield obtained was 95% when ethylene dichloride was used as a solvent and triethylbenzylammonium (TEBA) was used as phase-transfer catalyst.

In the case of p-cumidine, changing the molar ratio with respect to chlorocarbonylsulfenyl chloride from 1:1.04 to 1:1.73 M (entry 2; Table 1) lowered the yield from 95% to 35%, indicating an unfavorable effect on enhancing concentration of chlorocarbonylsulfenyl chloride. A change in molar ratio of phase-transfer catalyst TEBA (0.22 mM) against p-cumidine (1 M) to 0.05 mM: 1.0 M and 0.10 mM: 1.0 M (entries 3 and 4; Table 1) lowers the yield from 95% to 36% and 66% respectively, indicating

Table 1. Effect of phase transfer catalyst (PTC) and solvents in the synthesis of Isoproturon (**1a**) [molar ratio of p-cumidine: chlorocarbonylsulfenylchloride 1:1.04]

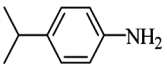
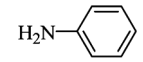
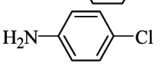
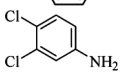
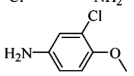
Entry	Phase transfer catalyst	Solvent	Yeild (%)
1	Triethylbenzylammonium chloride (0.22 mM)	Ethylene dichloride	95
2	Triethylbenzylammonium chloride (0.15 mM)	Ethylene dichloride	35*
3	Triethylbenzylammonium chloride (0.05 mM)	Ethylene dichloride	36
4	Triethylbenzylammonium chloride (0.10 mM)	Ethylene dichloride	66
5	Triethylene diamine (0.22 mM)	Ethylene dichloride	45
6	Dimethyl amino pyridine (0.22 mM)	Ethylene dichloride	85
7	without catalyst	Ethylene dichloride	20
8	Triethylbenzylammonium chloride (0.22 mM)	Tetrahydrofuron	52
9	Triethylbenzylammonium chloride (0.22 mM)	N-Methyl pyrrolidine	76
10	Triethylbenzylammonium chloride (0.22 mM)	Dimethyl sufoxide	28
11	Triethylbenzylammonium chloride (0.22 mM)	Dimethyl formamide	38

*Reaction using p-cumidine: **c**hlorocarbonylsulfenyl chloride 1.0 M:1.73 M.

the significant effect of phase-transfer catalyst concentration on the yield. A change of phase-transfer catalyst from TEBA to triethylene diamine and dimethylamino pyridine (entries 5 and 6; Table 1) lowered the yield from 95% to 45% and 85% respectively, while without catalyst (entry 7; Table 1) the yield was only 20%, suggesting TEBA as the most favorable phase-transfer catalyst.

A change of solvent from ethylene dichloride to tetrahydrofuran, N-methyl pyrrolidine, dimethylsulfoxide, and dimethylformamide (entries 8–11; Table 1) lowered the yields to 52%, 76%, 28%, and 38%, respectively, suggesting ethylene dichloride as the most favorable solvent.

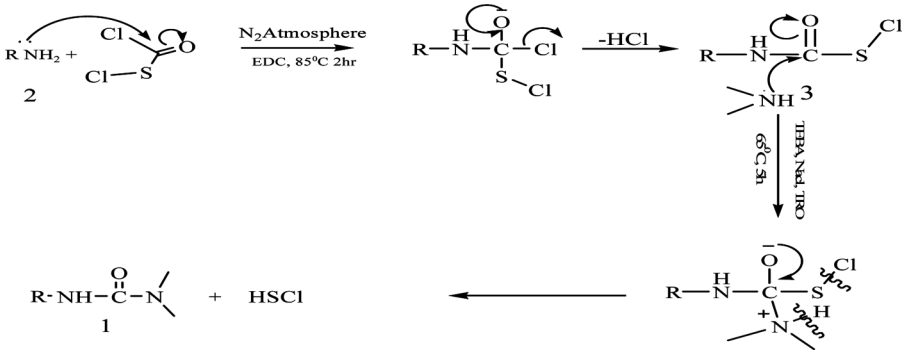
Table 2. Reaction conditions for synthesis of dimethylamine substituted aryl urea herbicides (**1a–e**)

Entry	Arylamine	2	Ratio 2/ccsc	Time (h)	3	Ratio 3/DMA	Time (h)	1	Yield (%)[y] (purity, %)[p]	Mp (°C)	Lit.[32]
1.		2a	1:1.04	2	3a	1:1.04	5	1a	94 (98.45)	158–158.5	155–156
2.		2b	1:1.15	4	3b	1:1.20	12	1b	90 (96.25)	133.8–134	131–134
3.		2c	1:1.10	2	3c	1:1.80	8	1c	92 (95.40)	173–174	–
4.		2d	1:1.20	4	3d	1:1.15	5	1d	88 (94.00)	154–154.5	153–155
5.		2e	1:1.05	8	3f	1:1.20	12	1e	90 (96.00)	125–126.5	126–127

2: arylamine (2a: para cumidine; 2b: aniline; 2c: para chloroaniline; 2d: 3,4-dichloroaniline; 2e: 3-chloro-4-methoxy aniline); ccsc: chlorocarbonylsulfenyl chloride; 1: dimethylamine substituted arylureas 1a: Isoproturon; 1b: Fenuron; 1c: Monuron; 1d: Diuron; 1e: Metoxuron.

[y]Yields of the isolated products.

[p]Purity determined by GC.



Scheme 1. General method for the preparation of dimethylamine substituted arylurea herbicides (**1a–e**): (**1a**) Isoproturon; (**1b**) Fenuron; (**1c**) Monuron; (**1d**) Diuron; (**1e**) Metoxuron (Commercial names of herbicides).

Other arylamines (**2b–e**) were similarly reacted using ethylene dichloride as solvent and TEBA as phase-transfer catalyst, while changing the other reaction conditions (Table 2).

The mechanism of this two-step reaction has been given in Scheme 1. The arylamine acts as nucleophile and attacks the carbonyl carbon of chlorocarbonylsulfenyl chloride, yielding the intermediate arylcarbonylsulfenyl chloride (**3**), the carbonyl carbon of which is further attacked by nucleophilic nitrogen of dimethylamine, yielding arylureas (**1a–e**).

CONCLUSION

A convenient, cost-effective synthetic method for the preparation of dimethyl amine substituted arylurea herbicides (**1a–e**) has been developed. The reaction occurs under mild conditions in which the carbonylation of aryl amines (**2a–e**) with chlorocarbonylsulfenyl chloride has been carried out followed by reaction with aqueous dimethylamine, powerfully assisted by the phase-transfer reagent TEBA and ethylene dichloride as a solvent. The optimal conditions for the synthesis of different arylurea herbicides have been reported. Insertion of a carbonyl group without using carbon monoxide gas is an advantage of this method.

EXPERIMENTAL

All chemicals (p-cumidine, aniline, 4-chloroaniline, 3,4-dichloroaniline, 3-chloro-4-methoxy aniline, ethylene dichloride, tetrahydrofuron, dimethylsulfoxide, dimethyl formamide, dimethylaminopyridine, TEBA, triethylene diamine) were purchased from Merck, India, and perchloromethyl mercaptan was doneted by India Pesticides, Lucknow, India. Melting points were determined on a paramount digital melting-point instrument, and gas chromatographic (GC) analyses were performed on a Thermo Fischer GC model GC-1000. ^{1}H NMR spectra were obtained on a Bruker Avance 400 spectrometer. Mass and exact mass spectra were recorded on a Perkin-Elmer mass spectrometer.

General Procedure for the Synthesis of 3-(4-Isopropyl-phenyl)-1,1-dimethylurea (Isoproturon, 1a)

Chlorocarbony sulfenyl chloride (34 g, 0.26 M) was added dropwise over 45–50 min to a stirred solution of p-cumidine (34 g, 0.25 M) in ethylene dichloride (200 ml) under vigorous reflux in a nitrogen atmosphere. The reaction was mildly exothermic, and the progress of the reaction was monitored by GC. After the addition, the reaction mixture was maintained at ~85 °C for an additional 2 h followed by distillation of ethylene dichloride (50 ml) under a vacuum to remove dissolved hydrochloric acid. The reaction mixture was diluted with ethylene dichloride (100 ml) and phase-transfer catalyst triethylbenzylammonium chloride (0.05 g, 0.22 M), sodium chloride (15 g, 0.24 M) and antifoaming agent turkyredoil (0.1 g) were added. A 10% aqueous solution of dimethylamine (120 g, 0.27 M) was added dropwise at 60–65 °C over 1 h. The progress of the reaction was monitored by GC. After the addition, the reaction mixture was maintained for an additional 5 h, followed by filtration and layer separation. The organic layer was collected, dried over sodium sulfate, and concentrated under a vacuum. The crude product was quenched in a pool of cold ethanol followed by crystallization, filtration, and drying to obtain colorless needles of 3-(4-isopropyl-phenyl)-1,1-dimethylurea (isoproturon, **1a**, Fig. 2); yield: 49.60 g (94%); 98.45% purity (GC), mp: 158–158.5 °C (lit.[32]).

^{1}NMR (200 MHz)[18]: $\delta = 1.22$ (d, J = 6.6 Hz, 6H, 2 × CH3), 2.79–2.92 (m, 1H, CH), 3.01 (S, 6H, 2 × CH3), 6.40 (br s, 1H, NH). 7.14 (d, $J = 8.8$ Hz, 2H, 2 × ArH), 7.28 (d, $J = 8.8$ Hz,2H, 2 × ArH).

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).

3-Phenyl-1,1-dimethylurea (Fenuron, 1b)

Yield: 42.65 g (90%); 96.25% purity (GC), colorless needles, mp: 133.5–134 °C (lit.[32]).

^{1}NMR (200 MHz)[17,18]: $\delta = 2.99$ (s, 6H, 2 × CH3), 6.51 (br s, 1H, NH), 7.01 (appt, $J = 7.2$ Hz, 1H, ArH), 7.26 (t, $J = 7.6$ Hz, 2H, 2 × ArH), 7.38 (d, $J = 7.6$ Hz, 2H, 2 × ArH).

MS (E1, 70 ev): m/z (%) = 164 (57) [M+], 119 (11), 91 (5), 72 (100) 65 (7).

3-(4-Chlorophenyl)-1,1-dimethylurea (Monuron, 1c)

Yield: 45.65 g (92%), 95.4% purity (GC), colorless needles, mp: 173–174 °C (lit.[32]).

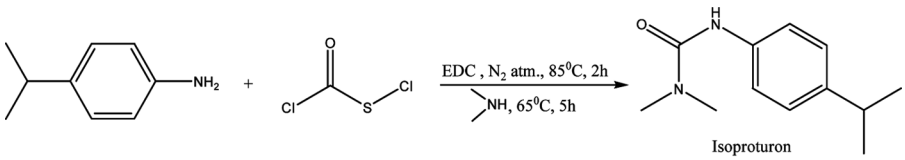


Figure 2. Preparation of Isoproturon.

^{1}NMR (200 MHz)[17,18]: δ = 3.00 (s, 6H, 2 × CH3), 6.40 (br s, 1H, NH), 7.21 (d, J = 8.8 Hz, 2H, 2 × ArH), 7.31 (d, J = 8.8 Hz, 2H, 2 × ArH).

MS (E1, 70 eV): m/z (%) = 198 (30) [M+], 153 (9), 73 (6), 72 (100)).

3-(3,4-Dichlorophenyl)1,1-dimethylurea (Diuron, 1d)

Yield: 51.50 g, (88%), 94% purity (GC), colorless needles, mp: 154–154.5 °C (lit.[32]).

^{1}NMR (200 MHz)[17,18]: δ = 3.00 (s, 6H, 2 × CH3), 6.42 (br s, 1H, NH), 7.19–7.21 (m, 1H, ArH), 7.22–7.30 (m, 1H, ArH), 7.59 (s, 1H,ArH).

MS (E1, 70 ev): m/z (%) = 232 (17) [M+], 189 (11), 187 (18), 124 (10), 73 (6), 72 (100), 44 (7).

3-(3-Chloro-4-methoxy-phenyl)1,1-dimethylurea (Metoxuron, 1e)

Yield: 60.50 g, (92%), 96% purity (GC), colorless needles, mp: 125–126.5 °C (lit.[32] 124–127 °C).

^{1}NMR (400 MHz)[17,18]: δ = 3.05 (s, 6H, 2 × CH3), 6.95 (dr s, 1H, NH), 7.17 (m, 1H, ArH), 7.34 (d, 1H, ArH).

Chlorocarbonylsulfenylchloride[34]

Trichloromethanesulfenyl chloride (294 ml, 500 g, 2.7 mol) was taken in a 2 L reaction flask equipped with reflux condenser, thermometer, and stirrer. A mixture of water (54 ml, 3.0 M) in concentrated sulfuric acid (620 ml) was added dropwise over 3 h. The heterogenous mixture was vigorously stirred for 6 h at 45–50 °C as HCl evolved and then stirred overnight at 25 °C to ensure complete conversion of perchloromethylmercaptan (trichloromethane sulfenyl chloride) (PCMM) to chlorocarbonyl sulfenyl chloride (CCSC). The progress of the reaction was monitored by GC. The upper phase (280 g, 80%) was separated and distilled through a column, bp 98–101 °C (lit.[34] bp 98 °C) to provide typically 230 g (65%) of the clear light yellow liquid of chlorocarbonylsulfenyl chloride.

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