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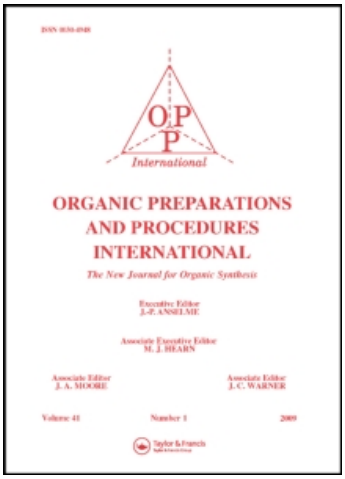

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NEW METHOD FOR SYNTHESIS OF *S*-METHYL-*N*-ARYLTHIOCARBAMATES

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NEW METHOD FOR SYNTHESIS OF *S*-METHYL-*N*-ARYLTHIOCARBAMATES

Submitted by (07/19/01)

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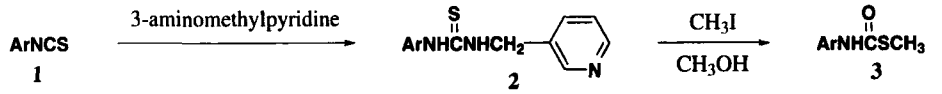
Thiolcarbamate herbicides such as triallate, diallate and S-ethyl-N-ethylthiolcyclohexane-carbamate[1] have strong activity against certain plants. Unfortunately, many of these compounds also have some, albeit weak, herbicidal activity on some crop plants. To promote the selectivity and extend the application of these herbicides, a series of effective antagonistic agents, S-methyl-N-arylthiocarbamates were designed to reduce or eliminate injury of thiolcarbamate herbicides to the desired crop plants while maintaining the herbicidal action on the weeds to be controlled.[2] Usually, S-methyl-N-arylthiocarbamates are prepared by introducing carbon monoxide to a mixture of $PhNH_2$, Me_2S_2, Et_3N and MeCN in a high-pressure kettle using Se[3-5] as catalyst. This method is laborious and requires forcing conditions. We report herein a much more practical and economical method to synthesize S-methyl-N-arylthiocarbamates.

Aryl isothiocynates (**1a-f**) readily reacted with 3-aminomethylpyridine to give N-aryl-N'-(3-pyridylmethyl)thioureas (**2a-f**) in nearly quantitative yields. The products were then treated directly with methyl iodide in CH_3OH at reflux to give S-methyl-N-arylthiocarbamates (**3a-f**). Surprisingly when benzylamine was used, S-methyl-N-benzyl-N'-phenylisothiourea was obtained in good yield (70%) instead of the substituted thiocarbamate. Presumably, 3-aminomethylpyridine is a better leaving group. In addition, 1.5, 2.5 and 3.5 equivalents methyl iodide were used in preparing **3f**. Although the yields were all low, the unavoidable loss of methyl iodide under reaction conditions was not the cause of low yield, since only 1.5 equivalent methyl iodide was needed in the formation of S-methyl-N-benzyl-N'-phenylisothiourea when benzylamine was used.



a) Ar = 4-fluorophenyl
b) Ar = 3,4-difluorophenyl
c) Ar = 2,3,4-trifluorophenyl
d) Ar = 3-chloro-4-fluorophenyl
e) Ar = 4-chlorophenyl
f) Ar = phenyl

EXPERIMENTAL SECTION

Infrared spectra were obtained on a Nicolet FT-IR-20SX spectrometer using KBr disks; Mass spectra were recorded on a Hitachi M80 instrument; and ^1H NMR spectra were taken on a

Brucker WP100SY(500 MHz) spectrometer with $CDCl_3$ or D_2O as solvent and TMS as internal standard. Melting points were measured using a digital melting point apparatus made in Shanghai Physico-optical Apparatus Co.Ltd. Elemental compositions were obtained by using an Italian MOD.1106 analyzer. All reactions were monitored using Thin Layer Chromatograph on silica plate.

N-Aryl-N'-(3-pyridylmethyl) Thioureas (2a-f). *General Procedure.*- To a solution of 3-aminomethylpyridine 1.08g (0.01 mol) in 20 mL of ethanol was added dropwise the aryl isothiocyanate (0.01 mol) over a period of 10 min. The reaction mixture was stirred for 0.5 hr at room temperature. The precipitated product formed in nearly quantitative yield was collected, washed and used in the next step without further purification (uncorrected mp, **2a**, 158-159°; **2b**, 147-148°; **2c**, 142-143°; **2d**, 165-166°; **2e**, 191-192°; **2f**, 151-152°).

S-Methyl-N-arylthiocarbamate (3a-f). *General Procedure.*- To a solution of the crude thiourea **(2a-f)** (0.005 mol) in 50 mL of methanol was added methyl iodide 4.26g (0.03 mol). The mixture was heated at reflux for 24 hrs. The solvent was removed under vacuum and the resulting crude products were recrystallized from H_2O to give products as white solids (see Table).

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Cmpd	Yield[a] (%)	mp (°C) (lit. mp)	IR (cm^{-1}) CO NH	^1H NMR (δ)	MS (M^+)	Elemental Analysis (Found) C	H	N
3a	57	85-87	1650 3300	2.34(s, 3H), 7.09(t, 2H), 7.60(m, 2H)	185	51.88 (52.00)	4.35 (4.46)	7.56 (7.66)
3b	46	120-122	1650 3300	2.35(s, 3H), 7.26(m, 2H), 7.68(m, 1H)	203	47.29 (47.32)	3.47 (3.54)	6.89 (6.85)
3c	45	107-109	1680 3300	3.36(s, 3H), 7.21(m, 1H), 7.66(m, 1H)	221	43.44 (43.53)	2.73 (3.84)	6.33 (6.41)
3d	54	128-129	1670 3350	2.41 (s, 3H), 7.06(m, 1H), 7.32(m, 1H), 7.41(m, 1H)	219	43.73 (43.56)	3.21 (3.11)	6.38 (6.29)
3e	59	137-138 (139)	1650 3300	----	201	----	----	----
3f	38	82-83 (83-84)	1650 3350	----	167	----	----	----

a) The yield refers to the second step only. The preparation of thiourea (first step) is so facile that the yields for this step are nearly quantitative. Thus, the overall yield for both steps is nearly equal to that for the second step.

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A HIGH YIELD, SELECTIVE SYNTHESIS OF 1,3,5-TRIMETHOXYBENZENE

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Methods for the introduction of methoxy substituents into aryl rings are important because of the use of methoxy compounds as intermediates for the synthesis of pharmaceutical products. Thus, 1,3,5-trimethoxybenzene (**2**) has been utilized extensively to prepare vasodilator agent buflomedil,[1,2] other novel drugs[3-5] and new compounds.[6,7] Moreover, the demethylation of methyl aryl ethers is an effective approach for the preparation of other phenolic compounds, *e.g.* the demethylation of **2** provides a direct route to phloroglucinol.[8,9] Although the direct preparations of **2** from 1,3,5-tribromobenzene (**1**) by displacement of bromide by methoxide have been reported, both the copper (I)-methyl formate catalyzed system[10] and the copper (II)-carbon dioxide-catalyzed system[11] are undesirable owing to the long reaction time and lower yields (81%[10] and 65%[11]) and selectivity. In general, aromatic nucleophilic substitution provides a useful route to many functionalized aromatic compounds. However, the lack of selectivity and the use of solvents such as hexamethylphorous triamide (HMPT), dimethylformamide (DMF) and pyridines and of copper-catalysts characterize the methoxylation of non-activated aryl