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THE INTRODUCTION OF A NEW SULFAMOYLATION REAGENT: N-CARBO-(TRIMETHYLSILYLOXY)SULFAMOYLCHLORIDE. VERSATILE SYNTHESES OF 3-AMINO-4-N-ALKYL AND 3-AMINO-2-N-ALKYL-5-ARYLOXY-1,2,4,6-THIATRIAZINE-1,1-DIOXIDES.

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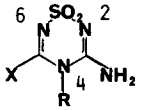
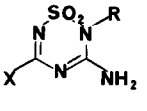
The use of a new sulfamoylation reagent, N-carbo-(trimethylsilyloxy)sulfamoyl chloride (3) has led to an abbreviated and high yielding preparation of 3-amino-4-N-alkyl-5-aryloxy-1,2,4,6-thiatriazine-1,1-dioxides (1). A related approach to the 2-N-alkyl isomer (2) is described.

N-Alkyl-1,2,4,6-thiatriazine-1,1-dioxides are compounds of considerable interest due to their herbicidal[1], fungicidal[2] and histamine H_2-antagonist[3,4] activity. We wish to report the development of efficient preparations for 3-amino-4-N-alkyl-5-aryloxy-1,2,4,6-thiatriazine-1,1- dioxides (1, where X is m-cresol) and the related 2-N-alkyl isomers (2, where X is m-cresol). Furthermore, our preparation of 1 introduces the use of a readily prepared, protected derivative of sulfamoyl chloride: N-carbo-(trimethylsilyloxy)sulfamoyl chloride(3). This reagent should be of general utility in the preparation of a wide variety of S and N containing heterocycles.

Our methodology has proved to be advantageous for the synthesis of both 4-N-alkyl and 2-N-alkyl isomers substituted with sterically demanding



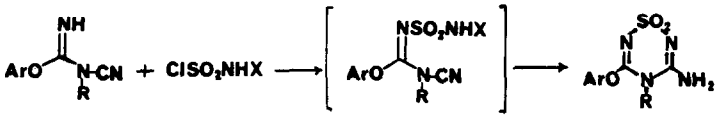
1



2

3

alkyl groups. In work reported previously[5], the 4-N-isopropyl derivative of 1 (where X is methylthio) could not be prepared[5a] and the 2-N-isopropyl derivative of 2 (where X is methylthio) was available in low yield (6%)[5b]. We have obtained yields of 81% and 54%, respectively for the corresponding isopropyl derivatives of 1 and 2 (where X is m-cresol).



4a-c 5 X= H 3 X= $CO_2Si[CH_3]_3$ 6 1a-c

a: R= $CH[CH_3]_2$, Ar= 3-$CH_3C_6H_4$
b: R= $[CH_2]_3CH_3$, Ar= 3-$CH_3C_6H_4$
c: R= $CH[CH_3]_2$, Ar= 4-$NO_2C_6H_4$

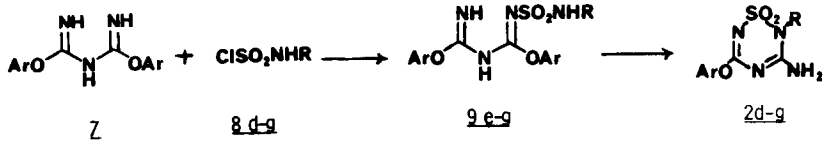
The scheme for the synthesis of 1 envisioned the cyclization of readily available N-cyano-N-alkyl pseudoureas 4a-c[6] with sulfamoyl chloride (5). However, we found the preparation of 5 (by the addition of one equivalent of water to chlorosulfonyl isocyanate[7]) to be inconvenient on a small scale and the purification of bifunctional 5 by distillation resulted in a low yield. Our solution to this problem was the development of a convenient substitute for 5, N-carbo(trimethylsilyloxy)sulfamoyl chloride (3).

Reagent 3 was available from the addition of one equivalent of 2-(trimethylsilyl)ethanol to chlorosulfonyl isocyanate in a variety of solvent mixtures (carbon tetrachloride, 4:1 carbon tetrachloride:dichloromethane and 4:1 carbon tetrachloride:cyclohexane). The initial adduct was detected by ^1H NMR[8], but during the removal of solvent under the usual conditions (~20 mm Hg, 40°) the elimination of ethylene occurred to give 3[9].

$$ClSO_2NCO + HO(CH_2)_2SiMe_3 \longrightarrow ClSO_2NHCO_2(CH_2)_2SiMe_3 \xrightarrow{-CH_2CH_2} ClSO_2NHCO_2SiMe_3$$

3

Sulfamoylation of 4a and 4b with a mixture of one equivalent each of freshly prepared 3 and triethylamine in dichloromethane gave 6. Compound 6 was deprotected and cyclized *in situ* by the addition of an excess of water with vigorous stirring. Heterocycles 1a and 1b[10] precipitated from the reaction mixture in excellent yield (see Table). Due to the decomposition of 4c by triethylamine, 1c was prepared by the addition of 0.5 equivalent of 3 to 4c and the product isolated by column chromatography after hydrolysis.



7 8d-g 9e-g 2d-g

Ar= 3-$CH_3C_6H_4$, R= d: CH_3, e: $CH[CH_3]_2$, f: $[CH_2]_3CH_3$, g: C_6H_{11}

The preparation of 2 followed in analogous fashion from imino bis[(3-methylphenyl)carbimidic acid] (7)[11]. Sulfamoylation of 7 with one equivalent of N-methylsulfamoyl chloride (8d)[12] and triethylamine in tetrahydrofuran gave 2d directly in quantitative yield. Similar treatment of 7 with the higher alkyl derivatives 8e-g[12] gave only the adducts 9e-g. These derivatives of 9 were cyclized with two equivalents of sodium hydride in tetrahydrofuran at room temperature to heterocycles 2e-g in good yield (see Table). The reaction time for the conversion of 9 to 2 varied directly with the increasing steric bulk of the N-alkyl group[13]. A similar steric inhibition was observed in cyclizations with N-alkylsulfamoyl derivatives of isothiobiuret similar to 9 (where ArO was the alkylthio group)[5b].

Table

		R	Ar	mp	Yield (%)
1	a	$CH(CH_3)_2$	$3\text{-}CH_3C_6H_4$	>250°	86
	b	$(CH_2)_3CH_3$	$3\text{-}CH_3C_6H_4$	208-213°	81
	c	$CH(CH_3)_2$	$4\text{-}NO_2C_6H_4$	>250°	42
2	d	CH_3	$3\text{-}CH_3C_6H_4$	>250°	100
	e	$CH(CH_3)_2$	$3\text{-}CH_3C_6H_4$	190-191°	54
	f	$(CH_2)_3CH_3$	$3\text{-}CH_3C_6H_4$	171-173°	80
	g	C_6H_{11}	$3\text{-}CH_3C_6H_4$	216-217°	35
9	e	$CH(CH_3)_2$	$3\text{-}CH_3C_6H_4$	107-110°	80
	f	$(CH_2)_3CH_3$	$3\text{-}CH_3C_6H_4$	100-102°	98
	g	C_6H_{11}	$3\text{-}CH_3C_6H_4$	141-143°	73

REFERENCES AND NOTES

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8. 90 MHz ^1H NMR (CCl_4, CH_2Cl_2 standard) δ : 8.8 (s, 1H), 4.3 (t, J=8Hz, 2H), 1.15 (t, J=8Hz, 2H) and 0.1 (s, 9H).
9. Reagent 3: One equivalent of 2-(trimethylsilyl)ethanol was added dropwise to a 2M solution of chlorosulfonyl isocyanate in 4:1 carbontetrachloride:hexane at ambient temperature. During the addition the reaction temperature rose from 25 to 40°C and the mixture was allowed to stir for 1h. After removal of the solvent, 3 was isolated in 100% yield as a low melting solid (m.p. <40°) and was used directly in sulfamoylations. 90MHz ^1H NMR (CCl_4, CH_2Cl_2 standard) δ : 8.6 (s, 1H) and 0.1 (s, 9H); IR 1740 (s), 1720 (s), 1410 (s), 1350 (s), 1160 (s) and 1050 (s).
10. Compounds 1a-c, 2d-g and 9e-g gave satisfactory combustion analyses. The ^1H NMR, infrared and mass spectra were in agreement with their proposed structures.
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13. The approximate times for the complete conversion of 9 to 2 were for 9e: 1h, 9f: 0.25h, 9h: 3h. Reactions were monitored by TLC.

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