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Synthesis of Arylsulfonylcarbamic Acid Derivatives Using a New, Phosgene-Free Method

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ABSTRACT: Arylsulfonylcarbamic acid esters, thioesters, and amides, 3, have been prepared via catalytic carbonylation of alkali metal salts of N-chloroarylsulfonamides, 1, and treatment of the reaction mixture with R^1XH (X=O, S, NR^2).

Arylsulfonylcarbamic acid derivatives, $ArSO_2NHC(O)XR^1$, 3, (Ar = aryl, X=O,S, R^1=alkyl, aryl; X=NR^2, R^1=H, alkyl, aryl R^2=H, acyl, heteroaryl) such as esters, thioesters and amides (ureas) exhibit useful biological properties which make them the active ingredients of various pharmaceutical and plant protective products. The blood sugar level reducing effect of certain arylsulfonylureas was discovered several decades ago and they are still in use [1, 2]. Other important arylsulfonylureas are those involving a substituted aryl (2-chlorophenyl, 2-methoxycarbonylphenyl) and a 4,6-disubstituted pyrimidinyl or triazinyl group [3]. These compounds show excellent herbicidal activity at an extremely low dosage (2-10g/ha). Some arylsulfonylcarbamates and -thiocarbamates are reported to help overcome the phytotoxic side effects of certain plant protective chemicals [4]. Recent investigations give hope that these compounds may be active against cancer-related diseases [5].

The best methods for the preparation of 3 are based on the direct or indirect application of phosgene, a highly toxic reagent [2, 6]. Recently we have reported that sodium or potassium salts of N-chlorosulfonamides can be catalytically carbonylated to yield arylsulfonyl isocyanates (eq. 1) [7].

$$\underset{\substack{(1)\\ M = Na^+,\ K^+}}{[ArSO_2NCl]M} + CO \xrightarrow[\text{solvent}]{\text{Pd-catalyst}} \underset{(2)}{ArSO_2NCO} + MCl \qquad (1)$$

We now report the synthesis of N-arylsulfonylcarbamic acid esters,

thioesters and amides via a general procedure, equation (2). The synthesis of **3** is carried out via catalytic carbonylation of N-chloroarylsulfonamidates (**1**) in an inert solvent (e.g. CH_2Cl_2, $ClCH_2CH_2Cl$, CH_3CN) at 20 - 60°C, in the presence of a palladium catalyst [$PdCl_2$, $PdCl_2(PhCN)_2$, $Pd_2(dba)_3$, (dba: dibenzylideneacetone)], followed by addition of R^1XH, usually, under cooling. Certain amines (R^2 is an electron withdrawing group, such as acetyl, ethoxycarbonyl, sym-triazinyl) can be added already to the starting mixture.

$$\underset{(1)}{[ArSO_2NCl]M} \xrightarrow[2.\ R^1XH]{1.\ CO,\ Pd\text{-}catalyst} \underset{(3)}{ArSO_2NHC(O)XR^1} + MCl \qquad (2)$$

$$(X = O,\ S,\ NR^2;\ M = Na^+ \text{ or } K^+)$$

Reactions (1) and (2) cannot be classified either as *reductive* [8, 9] or as *oxidative* [9] carbonylation process for neither an excess CO nor an oxidizing agent is necessary to accomplish the formation of the products. Therefore, they can be best depicted as *neutral* carbonylations because no change in the oxidation state of the nitrogen atom takes place during the reaction.

However, as the formation of the N-chloro compounds **1** is an oxidative step,

$$ArSO_2NH_2 + MOCl \longrightarrow [ArSO_2NCl]M + H_2O \qquad (3)$$

equations (3) and (1) or (2) make up a *two-step oxidative carbonylation* process. The relative stability of N-chloroarylsulfonamidates makes it possible to carry out these two reactions separately, which is not known in the case of simple aromatic amines.

Reaction (2) apparently occurs via the corresponding arylsulfonyl isocyanate as intermediate, eq. (1). The latter is presumably formed via carbonylation of an arylsulfonylnitrene coordinated to the palladium atom. Studies on the mechanism of this novel carbonylation are in progress.

Experimental

Solvents and reactants were dried to minimize hydrolytic side reactions. CO (99.95% purity) was used without purification.

General procedure, Version **A**: A 45 cm^3 stainless steel reactor (Parr Model 4712) was charged with 10 cm^3 CH_2Cl_2, 0.5 cm^3 CH_3CN, 0.01 mol potassium N-chlorosulfonamidate and 0.12 g $PdCl_2(PhCN)_2$, and pressurized with CO to 35 bar. The reactor was stirred and thermostated at 60°C for 1 hour, then, after cooling, the gas phase was removed and the yellow

Table 1

Synthesis of $ArSO_2NHC(O)XR^1$ via catalytic carbonylation of $[ArSO_2NCl]M$

	[ArylSO_2NCl]M	R^1XH	version	Yield of 3 (%)
a	[$PhSO_2$NCl]K	isopropanol	A	68
b	[4-CH_3PhSO_2NCl]Na	isopropanol	A	78
c	[2-ClPhSO_2NCl]K	ethanol	A	76
d	[2-ClPhSO_2NCl]K	allyl alcohol	A	72
e	[2-ClPhSO_2NCl]K	2-methyl-2-propanol	A	68
f	[2-ClPhSO_2NCl]K	benzyl alcohol	A	76
g	[2-ClPhSO_2NCl]K	2-chlorophenol	A	79
h	[2-ClPhSO_2NCl]K	cyclohexyl mercaptan	A	74
i	[2-ClPhSO_2NCl]K	butyl mercaptan	A	71
j	[4-CH_3PhSO_2NCl]K	hexamethyleneimine	A	71
k	[4-CH_3PhSO_2NCl]K	2-aminobenzotrifluoride	A	72
l	[2-ClPhSO_2NCl]K	2-aminobenzonitrile	A	68
m	[$PhSO_2$NCl]K	urethane	B	81
n	[$PhSO_2$NCl]K	acetamide	B	78
o	[4-CH_3PhSO_2NCl]K	urethane	B	84
p	[4-MePhSO_2NCl]K	acetamide	B	77
q	[2-BrPhSO_2NCl]K	2-amino-4-methoxy-6-methyl-1,3,5-triazine	B	68

reaction mixture was transferred under N_2 into a Schlenk tube. 0.01 mol of R^1XH in dry CH_2Cl_2 was added dropwise. (Amines of low basicity can be added in one portion.) The liquid phase was removed on a rotavapor and the solid residue was extracted with diethyl ether. Evaporation of the ethereal solution allowed to isolate 3 (X=O, S). In the isolation of ureas, 1,2-dichloroethane was preferred for the extraction. Version B: same as A, but R^1XH was added to the starting mixture.

Yields are shown in Table 1. The IR data of 3a-3q are collected in note [10]. In case of any uncertainty in the interpretation of the spectra, an MS-FAB analysis was also carried out.

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