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Uncatalyzed Friedel–Crafts Alkylation of Aromatic Compounds through Reactive Benzyl Cations Generated from *N*-Sulfamoylcarbamates

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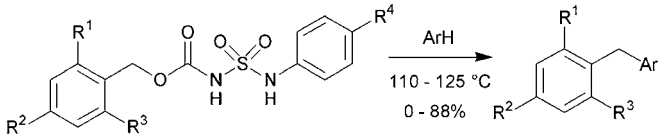
ABSTRACT



A new method for the generation of highly reactive benzyl cations by thermal decomposition of aryl-benzyl-sulfamoylcarbamates, obtained in a one-pot reaction from chlorosulfonyl isocyanate, is described. The generated cations alkylate aromatic compounds efficiently in the absence of catalysts.

Essentially "free" benzyl cations have been generated by thermolysis of *N*-benzyl-*N*-nitrosoamides[1] in nonsolvating solvents. These cations were spatially separated from the anions by an inert nitrogen molecule formed after thermal rearrangement of the nitrosoamide.[2] The poorly solvated, highly reactive cations can alkylate aromatic compounds in the absence of a catalyst.[3] Despite the reactivity of these cations, recombination of the ions usually predominates, due to rapid nitrogen diffusion. As a result, the yields of alkylation products are generally low (between 2% for 4-methylbenzyl and 26% for the more reactive 4-nitrobenzyl derivatives).[3] However, electron-rich heteroaromatic compounds provide up to 80% yield of solvent-derived products.[4,5]

Chlorosulfonylcarbamates of tertiary or allylic alkyl groups decompose at elevated temperature to alkylaminosulfonyl chlorides and CO_2.[6] It was expected that benzyl sulfamoylcarbamates would undergo a similar CO_2 extrusion reaction to yield benzylsulfamides.[7,8] Obviously, such reactions would also generate benzyl cations as reactive intermediates.

The new benzyl sulfamoylcarbamates **1**−**4** (Scheme 1) were prepared in one step by treatment of the corresponding benzyl alcohols with chlorosulfonyl isocyanate (CSI)[9] at −10 °C in THF, followed by the addition of 2 equiv of aniline or 4-chloroaniline, respectively (72−90% yield).

Sulfamoylcarbamates **1**−**4** are crystalline compounds, insensitive to hydrolysis and thermally stable up to 80 °C.

(1) Darbeau, R. W.; White, E. H.; Song, F.; Darbeau, N. R.; Chou, J. *J. Org. Chem.* **1999**, *64*, 5966−5978.
(2) White, E. H.; Field, K. W.; Hendrickson, W. H.; Dzadzic, P.; Roswell, D. F.; Paik, S.; Mullen, P. W. *J. Am. Chem. Soc.* **1992**, *114*, 8023−8031.
(3) (a) Darbeau, R. W.; White, E. H. *J. Org. Chem.* **2000**, *65*, 1121−1131. (b) White, E. H.; Darbeau, R. W.; Chen, Y.; Chen, S.; Chen, D. *J. Org. Chem.* **1996**, *61*, 7986−7987.
(4) Darbeau, R. W.; White, E. H. *J. Org. Chem.* **1997**, *62*, 8091−8092.
(5) Additionally, the employed *N*-benzyl-*N*-nitrosoamides are thermolabile, sensitive to hydrolysis, and highly carcinogenic, thus preventing a general use of these compounds.
(6) LONZA-COR Publication *Chlorosulfonyl Isocyanate*, 2nd ed.; 1980.
(7) (a) Burke, P. O.; McDermott, S. D.; Hannigan, T. W.; Spillane, W. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1851−1854. (b) DuBois, G. E. *J. Org. Chem.* **1980**, *45*, 5373−5375.
(8) Buchs, J. Ph.D. Thesis, Universität Potsdam, Potsdam, Germany, 1999.
(9) For similar syntheses using CSI, see: (a) Dewynter, G.; Montero, J.-L. *C. R. Acad. Sci., Ser. II* **1992**, *315*, 1675−1682. (b) Muller, G. W.; DuBois, G. E. *J. Org. Chem.* **1989**, *54*, 4471−4473. Since CSI is known to be the most reactive isocyanate, this reagent must be handled with care. On the other hand, the sulfamoylcarbamates **1**−**4** exhibit low cytotoxicity (unpublished results).

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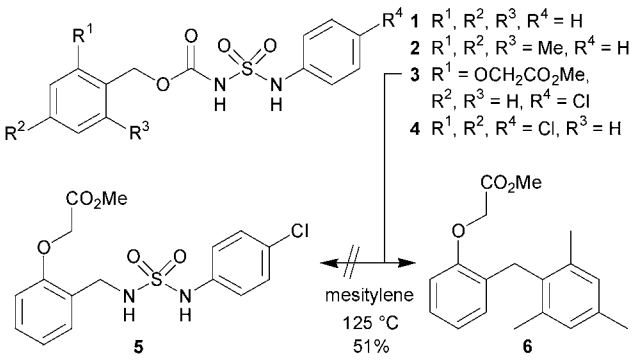
Scheme 1



Upon heating above 110 °C in mesitylene, *N*-sulfamoylcarbamate **3** began to decompose as indicated by gas evolution and formation of a dark precipitate. After 5 h at 125 °C, TLC analysis (silica gel, 1:15 EtOAc/hexanes) indicated the predominance of a nonpolar compound and the disappearance of the starting material, along with several highly polar species, which have yet to be identified. Two products were expected to have been formed by the thermal CO_2 extrusion of **3** in mesitylene: sulfamide **5** and benzylated mesitylene **6** (Scheme 1). Indeed, mesitylene derivative **6** was isolated as the major product in 51% yield.

Sulfamoylcarbamates **1**−**4** were reacted with several varyingly activated aromatic compounds (Scheme 2, Table 1), each serving either as a solvent or as a cosolvent (in combination with octane as an "inert" solvent). In every case

Scheme 2

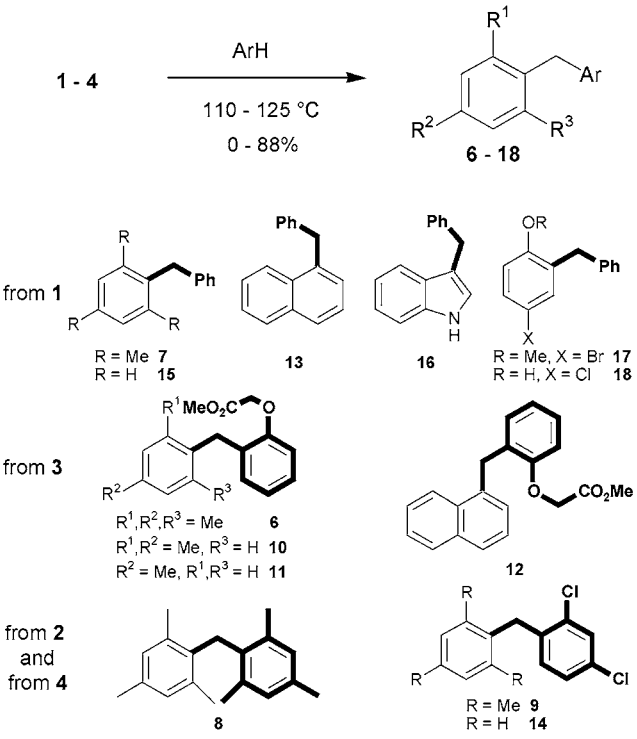


Table 1. Alkylation of Aromatic Compounds through Thermal Decomposition of Sulfamoylcarbamates

arene (equiv)	carbamate	*T* (°C)	product	yield (%)[a]	isomeric ratio
mesitylene (7)	**1**	115	**7**	71[b]	
mesitylene (1.1)[c]	**1**	127	**7**	15	
mesitylene (7)	**2**	115	**8**	20	
mesitylene (6)	**3**	125	**6**	51	
mesitylene (7)	**4**	120	**9**	88	
mesitylene (7)	**20**[d]	120	**7**	26[e]	
m-xylene (10)	**3**	118	**10**	62	*o,p*-**10**:*o,o*-**10** = 6:1
toluene (11)	**3**	112	**11**	40	*o*-**11**:*p*-**11** = 2:1
benzene (50)	**4**	80	**14**	<2[f]	
benzene (56)	**1**	115[g]	**15**	25	
benzene (5)[c]	**1**	123	**15**	2	
naphthalene (8)	**3**	125	**12**	57	α-**12**:*β*-**12** = 4:1
naphthalene (2)[c]	**1**	127	**13**	10	α-**13**:*β*-**13** = 8:1
indole (3)	**1**	125	**16**	25	
pyridine (12)	**1**	114			
benzonitrile (8)	**4**	120			
benzaldehyde (9)	**4**	123			
4-Br-anisole (7)	**1**	122	**17**	41	
4-Br-anisole (3)[h]	**1**	123	**17**		
4-Cl-phenole (6)[i]	**1**	110	**18**	20	

[a] Yields refer to isolated and purified products. [b] Dibenzyl-mesitylene (**19**) was isolated in 9% yield. [c] Octane was used as an inert solvent. [d] **20** = Benzyloxycarbonyl chloride ((*Z*)-Cl). [e] Benzyl chloride was obtained as the major product (42%). [f] After 72 h at 80 °C. [g] Reaction was performed in a screw-capped, thick-walled flask. [h] Chlorobenzene was used as a solvent. [i] Benzyl 4-chlorophenyl ether (**21**) was isolated as the major product (25%).

in which alkylation of the arene was achieved, monoalkylated aromatic compounds were obtained as major products.[10] The ratio of mono- to polyalkylated products was dependent upon the relative amount of aromatic solvent to sulfamoylcarbamate: With a ratio of 6−11:1 (arene/sulfamoylcarbamate), up to 88% monoalkylation and 0−9% dialkylation were observed. A large excess (~50:1) of the arene gave exclusively the monoalkylation product. The reaction also occurred when nearly equimolar amounts of carbamate and arene were heated in octane as an inert, high-boiling solvent, but the yields were significantly lower under these conditions (entries 1 and 2, 9 and 10, and 12 and 13 in Table 1).

Weakly activated aromatic compounds (mesitylene, toluene, xylene, naphthalene) reacted with carbamates **1**−**4** to alkylation products **7**−**12** in moderate to excellent yields (20−88%). Benzene was not alkylated in a reasonable quantity under normal pressure (<2% of **14**), due to its low boiling point. However, in a screw-capped, thick-walled flask, it was possible to obtain diphenylmethane (**15**) in 25% yield at 115 °C. The isomeric ratio of compounds **10**−**12** was in agreement with the general rules of second and third substitutions of aromatic compounds. The ratio of *o,p*- and *o,o*-**10** was 6:1; the ratio of *o*- and *p*-**11** was 2:1, and that of α- and *β*-**12** was 4:1. The isomeric ratio of the naphthalene analogues α- and *β*-**13** was 8:1 when the reaction was carried out in octane, though **13** was obtained in comparatively low yield (10%). Electron-rich heteroarenes such as indole reacted

(10) This is particularly interesting in cases where monoalkylated products are difficult to obtain by standard Friedel−Crafts alkylation. See: Tsuchikawa, H.; Iwamoto, Y. (Nisshin Oil Mills, Ltd.) JP 11 228,459, 1999; *Chem. Abstr.* **1999**, *131*, 171853h.

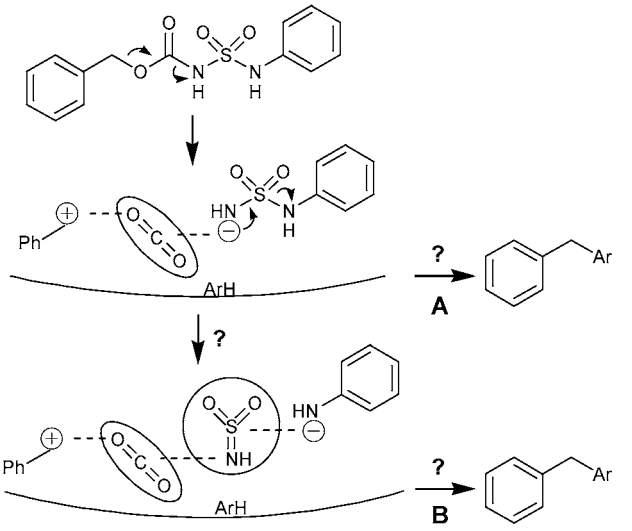
with **1** to generate 3-benzylindole (**16**) in 25% yield. Deactivated aromatic compounds (pyridine, benzonitrile, benzaldehyde) were not alkylated under these conditions (Table 1).[11] Activated aromatic compounds (4-bromoanisole, 4-chlorophenol), on the other hand, were suitable substrates for the reaction with sulfamoylcarbamates (Table 1). As expected from the general reactivity of halophenols or haloaryl ether, C-alkylation occurred ortho to the oxygen, providing **17** and **18**[12] in 41 and 20% yields, respectively. In the case of 4-chlorophenol, O-alkylation strongly competed with C-alkylation. Consequently, benzyl-4-chlorophenyl ether (**21**) was obtained as major product (25%). The alkylation of arenes with **1**−**4** in octane as an inert solvent is sluggish due to the low solubility of the sulfamoylcarbamate. Since haloarenes do not react ortho to the halogen, chlorobenzene was used as an "inert" solvent, in which the sulfamoylcarbamates exhibited better solubility. However, alkylation of 4-bromoanisole with carbamate **1** was suppressed when the reaction was performed in chlorobenzene.

It is known that benzyloxycarbonyl chloride ((*Z*)-Cl, **20**) decomposes slowly at ambient or elevated temperature to benzyl chloride under CO_2 elimination. Considering that an unsolvated benzyl cation is formed in this process, mesitylene was treated with (*Z*)-Cl under the same reaction conditions as employed for the reaction of mesitylene with **1**. Indeed, benzylmesitylene **7** (26%) and benzyl chloride (42%) were obtained as major products (Table 1). However, the yield of alkylated product was substantially lower with (*Z*)-Cl than with carbamate **1**.

Although a detailed study of the reaction mechanism has not yet been carried out, it was assumed that separation of cation and anion by one (or more) neutral molecule(s) occurs during decomposition of sulfamoylcarbamates, similar to the thermolysis of benzyl-*N*-nitrosoamides (Scheme 3). In an initial step, the carbamate moiety is cleaved into the benzyl cation, CO_2, and the sulfamide anion. This is indicated by the gas evolution observed during heating and by the mass peak for the $-NSO_2NHPh$ anion found when **1** was heated in the ionization chamber of a mass spectrometer (measured in the negative ion mode).

The major difference of the present method for generating carbocations from that reported[1] is the efficiency with which the aromatic solvents are alkylated. One reason for this increased alkylation ability might be the physicochemical properties of the neutral molecule: (1) CO_2 is less volatile than N_2, and thus has a longer lifetime between the separated ion.[13] (2) In contrast to N_2, CO_2 is a molecule with polar bonds and a complete separation of the cation (and/or anion)

Scheme 3



from CO_2 might not occur prior to the interaction of the cation with the π system of the aromatic solvent (pathway **A**). *This assumption, however, cannot explain why (Z)-Cl (**20**) gives significantly lower yields of alkylated product than sulfamoylcarbamate **1**.* An alternative explanation might be the formation of a second neutral species, sulfimide,[14] during heating (pathway **B**, Scheme 3).[15] The increased distance between cation and anion would create an additional hindrance for a rapid recombination of the ions. It is also possible that, depending on the substitution pattern of the sulfamoylcarbamate, both mechanisms shown in Scheme 3 may account for the reaction behavior of these carbamates.

A series of alkyl sulfamoylcarbamates (*tert*-butyl, neopentyl, cyclopentyl, cyclohexylmethyl) have been prepared and decomposed in the presence of mesitylene. In no case were alkylation products obtained. A fast β-elimination of a proton or steric hindrance might be responsible for their different reactivity.[16] Additionally, carbamoyl derivatives containing two arenes at the benzylic position, e.g., diphenylmethyl sulfamoylcarbamate, were not suitable for the alkylation of benzene or other arenes due to the lower electrophilicity of the diphenylmethyl cation.[17]

(11) Structures of products obtained by the interception of benzyl cations with the carbonyl or nitrile group were not determined. For some recent studies on this topic, see: Darbeau, R. W.; White, E. H.; Nunez, N.; Coit, B.; Daigle M. *J. Org. Chem.* **2000**, *65*, 1115−1120. Song, F.; Darbeau, R. W.; White, E. H. *J. Org. Chem.* **2000**, *65*, 1825−1829.

(12) Phenol **18** is used as a key precursor for the synthesis of a reversible inhibitor of the cytosolic phospholipase A_2: Burke, J. R.; Witmer, M. R.; Zusi, F. C.; Gregor, K. R.; Davern, L. B.; Padmanabha, R.; Swann, R. T.; Smith, D.; Tredup, J. A.; Micanovic, R.; Manly, S. P.; Villafranca, J. J.; Tramposch, K. M. *J. Biol. Chem.* **1999**, *274*, 18864−18871.

(13) Similar tendencies were found in the thermal decomposition of *N*-nitrosoamides and *N*-nitroamides where N_2 and the less volatile N_2O, respectively, act as neutral molecules. See ref 1.

(14) (a) Morgon, N. H.; Linnert, H. V.; Riveros, J. M. *J. Phys. Chem.* **1995**, *99*, 11667−11672. (b) Houk, K. N.; Strozier, R. W.; Hall, J. A. *Tetrahedron Lett.* **1974**, 897−900.

(15) Decomposition of **1** in a mass spectrometer by electron ionization afforded, among others, peaks at 262, 183, and 181, corresponding to *N*-benzyl-*N*′-phenylsulfamide (M − CO_2), *N*-benzylaniline (M − CO_2 −SO_2-NH), and *N*-benzylideneaniline (M − CO_2 −NH_3 −SO_2). The latter is probably produced by the oxidation of the benzyl cation. The molecular compositions of these fragments were established by high-resolution mass spectrometry. Although pathway **A** seems more likely, the preliminary mass spectrometric studies indicate that pathway **B** cannot be ruled out.

(16) For example, cyclopenene, derived from elimination from cyclopentyl sulfamoylcarbamate, was easily identified by its odor and, subsequently, by proton NMR. However, starting materials without β-protons such as neopentyl sulfamoylcarbamate yield three major products whose structures are currently unknown. These products are crystalline compounds, and efforts are underway to obtain suitable crystals for X-ray crystallography.

(17) Mayr, H.; Patz, M. *Angew. Chem.* **1994**, *106*, 990−1010.

We have developed a new method for the generation of benzyl cations. These cations can alkylate activated aromatic compounds in the absence of a catalyst. Further investigations into the scope and limitation of this reaction as well as mechanistic studies are in progress.

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Supporting Information Available: Experimental details and spectroscopic data of all compounds except **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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