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Unprecedented observation of sulfonamides in the transesterification of *N*-unsubstituted carbamates with sulfonyl chlorides

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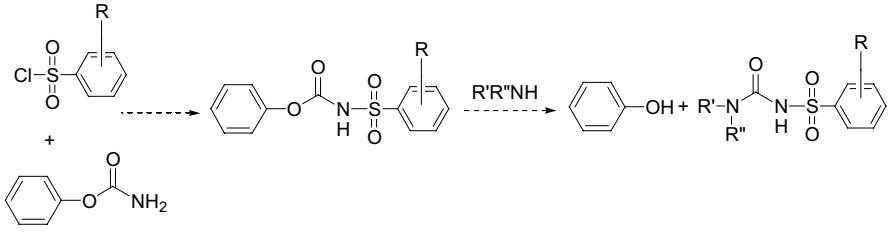
Abstract—Sulfonamides have been identified as by-products in the base-mediated transesterification of *N*-unsubstituted carbamates with sulfonyl chlorides to give the corresponding sulfonates. A proposed mechanism and the synthesis of hindered 2,6-disubstituted arylsulfonates via this method are also reported.

In a program aimed at developing methodology for the synthesis of diverse arrays of arenesulfonyl ureas, we considered the possibility of reacting arenesulfonyl chlorides with phenyl carbamate to produce arenesulfonyl phenyl carbamates. We envisaged that these intermediates could then be reacted with an array of amines to give the target arenesulfonyl ureas with phenol as a by-product (Scheme 1).

When benzenesulfonyl chloride **1** (1.3 equiv) was reacted with phenylcarbamate **2** in 1,4-dioxane in the presence of triethylamine (Et_3N), the reaction afforded benzenesulfonic acid phenyl ester **3** and benzenesulfonamide **4** (Scheme 2). The envisaged carbamate **5** was not observed. Similarly, the reaction conducted in tetrahydrofuran (THF) in the presence of sodium hydride (NaH) also afforded products **3** and **4**. The same reaction conducted in *N*,*N*-dimethylformamide (DMF) afforded **3** and the *N*-sulfonylamidine **6**.

A literature search subsequently revealed a publication in 1987 by Latif and co-workers concerning the transesterification reaction of *p*-toluenesulfonyl chloride with *N*-unsubstituted aryl carbamates bearing a nitroethenyl side chain using 1,4-dioxane as a solvent in the presence of Et_3N.[1] The corresponding sulfonates were reported as the only products. No accompanying sulfonamides were reported in this publication. Accordingly we decided to investigate further the reaction of benzenesulfonyl chloride **1** with substituted phenylcarbamates under the reported conditions. For this purpose substituted phenylcarbamates were synthesized following a literature procedure in which substituted phenols **7**–**11** were reacted with chlorosulfonyl isocyanate (CSI) followed by



Scheme 1.

Keywords: carbamates; transesterification; arylsulfonates; sulfonamides.
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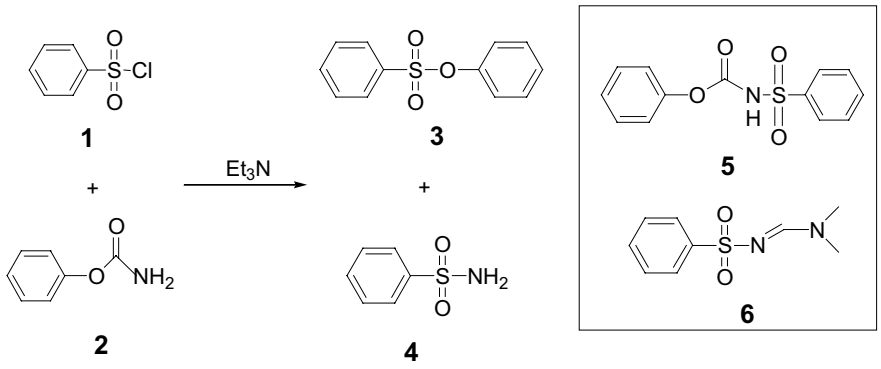
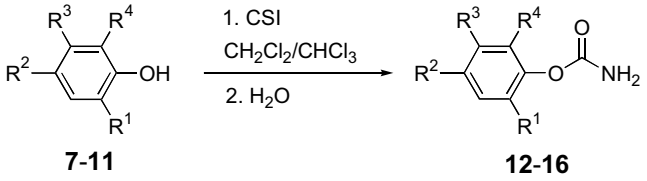


Scheme 2.



Scheme 3.

water hydrolysis of the resulting intermediate (Scheme 3).[2–4]

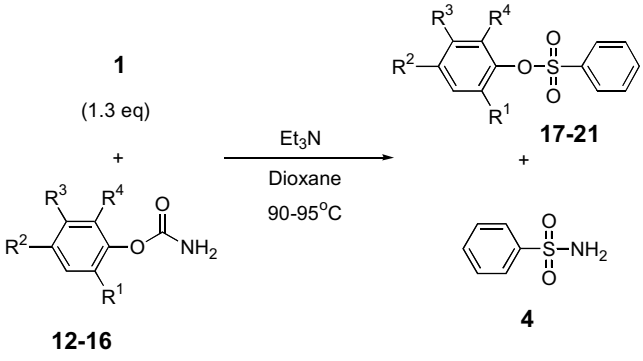
The substituted phenylcarbamates **12**–**16** were obtained in good yields (Table 1) and high purity as judged from the respective ^{1}H NMR spectra. No further purification was required. These carbamates were then reacted with benzenesulfonyl chloride **1** in the presence of Et_3N at 90–95 °C (Scheme 4). The results of these reactions are summarized in Table 2.

From the results in Table 2, it is evident that most of the reactions yielded mixtures of both the sulfonic acid phenyl esters and benzenesulfonamide. It is noteworthy that the reaction involving 4-methoxy-phenylcarbamate **16** afforded higher yields of both products in a relatively short time (entry 5). The longest reaction time (74 h) was that involving 2,6-dimethylphenylcarbamate **14** (entry 3). This is presumably due to the steric crowding imparted by the methyl groups at both *ortho* positions.

In order to account for the formation of both the sulfonates and benzenesulfonamide in these reactions, a proposed mechanism is depicted in Scheme 5.

Table 1. Preparation of the substituted phenylcarbamates **12**–**16** starting from phenols **7**–**11**

Entry	Phenol	R^1	R^2	R^3	R^4	Product (% yield)
1	**7**	CH_3	CH_3	H	H	**12** (49)
2	**8**	CH_3	H	CH_3	H	**13** (71)
3	**9**	CH_3	H	H	CH_3	**14** (83)
4	**10**	H	CH_3	H	H	**15** (96)
5	**11**	H	OCH_3	H	H	**16** (77)



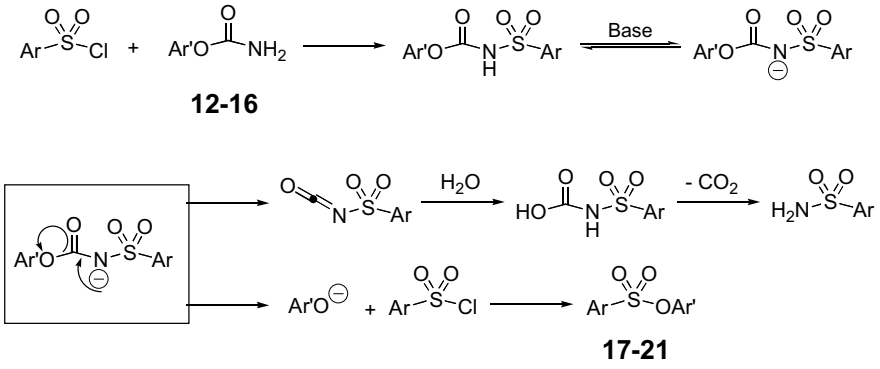
Scheme 4.

Phenylcarbamate presumably reacts with the arenesulfonyl chloride to give the expected arenesulfonyl phenyl carbamate. This species is subsequently deprotonated in situ, and the anionic intermediate collapses to form an arenesulfonyl isocyanate and a phenoxide anion. The former is hydrolyzed during the work-up to yield an arenesulfonamide, while the latter reacts with a

Table 2. Reactions of benzenesulfonyl chloride **1** with carbamates **12**–**16** at 90–95°C

Entry	Carbamate	R^1	R^2	R^3	R^4	Reaction time (h)	Product A (% yield)	Product B (% yield)
1	**12**	CH_3	CH_3	H	H	48	**17** (36)	**4** (30)
2	**13**	CH_3	H	CH_3	H	48	**18** (18)	**4** (36)
3	**14**	CH_3	H	H	CH_3	74	**19** (14)	**4** (41)
4	**15**	H	CH_3	H	H	1	**20** (37)	No product
5	**16**	H	OCH_3	H	H	1	**21** (50)	**4** (50)

A = sulfonic acid phenyl ester.
B = benzenesulfonamide.

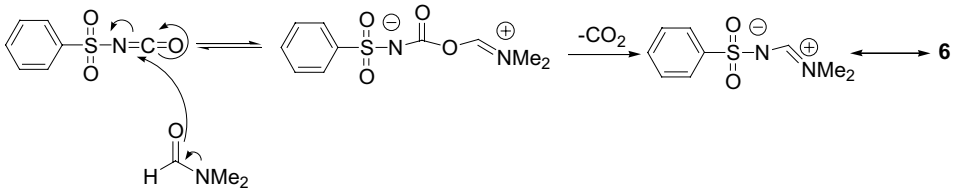


Scheme 5.

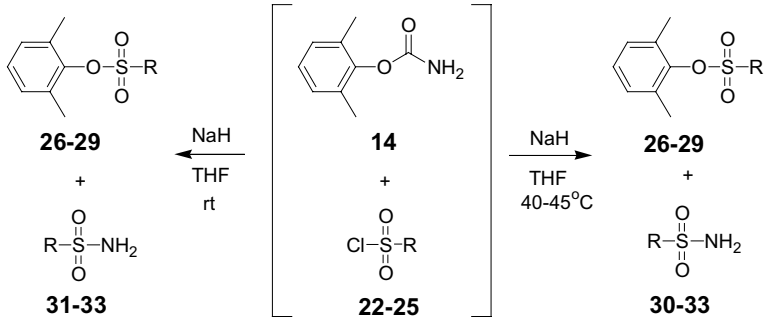
second molecule of arenesulfonyl chloride to yield an arenesulfonic phenyl ester.

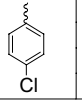
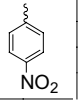
When DMF is used as the solvent, the intermediate sulfonyl isocyanate formed reacts further with DMF to produce **6** (Scheme 6). Presumably, the adduct formed between the arylsulfonyl isocyanate and DMF is not thermally stable, and its decarboxylation product is observed. A similar phenomenon was previously described with chloroformates.[5,6]

The long reaction time and low yield for the sulfonic acid phenyl ester **19** prompted us to investigate further the reaction of 2,6-dimethylphenylcarbamate **14** with other sulfonyl chlorides (Scheme 7). Initial attempts to react **14** with sulfonyl chlorides **22**–**25** in the presence of Et_3N at various temperatures (room temperature and 90–95 °C) in 1,4-dioxane and at 60–65 °C in THF were unsuccessful. We reasoned that the substrates and/or products decomposed at high temperature or that the reactions were taking too long to occur as was the case previously. As a result, we resorted to the use of NaH in THF and lower temperatures. The reactions proceeded within 4–5 h; the results are shown in Table 3. From the results in Table 3, it is evident that various sulfonamides and sulfonic acid esters can be obtained (albeit in low yields) utilizing this reaction in the presence of sodium hydride.[7]



Scheme 6.



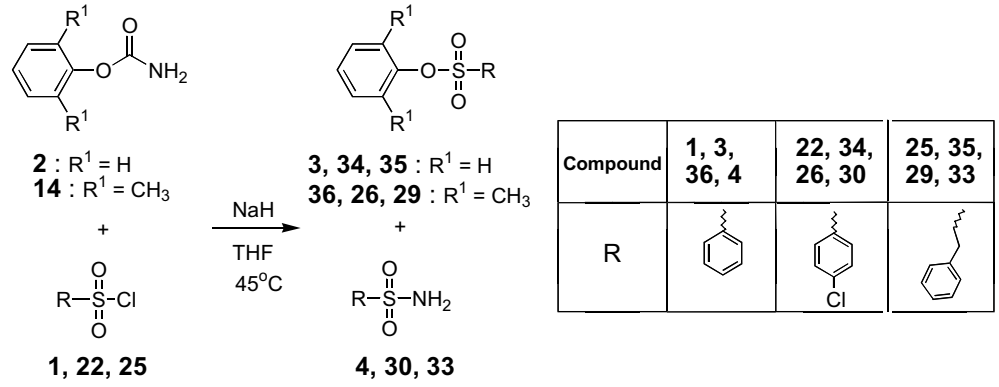
Compound	22, 26, 30	23, 27, 31	24, 28, 32	25, 29, 33
R				

Scheme 7.

Table 3. Reactions of carbamate **14** with sulfonyl chlorides in THF using NaH as the base

Entry	Sulfonyl chloride	Reaction time (h)	Reaction temperature (°C)	Product A (% yield)	Product B (% yield)
1	**22**	4	40–45	**26** (39)	**30** (10)
2	**23**	4	40–45	**27** (16)	**31** (26)
3	**24**	4	40–45	**28** (32)	**32** (13)
4	**25**	5	40–45	**29** (21)	**33** (29)
5	**22**	14	rt	**26** (46)	No product
6	**23**	14	rt	**27** (28)	**31** (14)
7	**24**	15	rt	**28** (41)	**32** (27)
8	**25**	14	rt	**29** (30)	**33** (29)

A = sulfonic acid ester.
B = sulfonamide.



Scheme 8.

Table 4. Reactions of carbamates **14** with sulfonyl chlorides (2 equiv) at rt in THF using NaH as the base

Entry	Sulfonyl chloride	Carbamate	Reaction time (h)	Product A (% yield)	Product B (% yield)
1	**1**	**2**	16	**3** (44)	**4** (17)
2	**22**	**2**	16	**34** (90)	**30** (69)
3	**25**	**2**	16	**35** (26)	**33** (12)
4	**1**	**14**	16	**36** (90)	**4** (61)
5	**22**	**14**	16	**26** (99)	**30** (29)
8	**25**	**14**	16	**29** (55)	**33** (22)

A = sulfonic acid ester.
B = sulfonamide.
Product yields are based on phenylcarbamates.

In the light of these results, we became interested in optimizing the yields of arenesulfonic acid esters, especially in the case of hindered arylsulfonates. Following the mechanism given in Scheme 5, this could be easily achieved by using 2 equiv of arenesulfonyl chloride with respect to the phenylcarbamate. A last series of experiments was carried out at 45 °C in THF, using NaH as a base (Scheme 8).[8] The results listed in Table 4 show the expected noticeable increase in yields of arenesulfonic acid ester.

In summary, we have shown that sulfonamides can be obtained from the transesterification reaction of *N*-unsubstituted carbamates with sulfonyl chlorides. Moreover, this procedure has potential for the efficient synthesis of hindered sulfonates exemplified by 2,6-disubstituted arylsulfonates. Although a number of these reactions give low yields, there is scope for optimization studies aimed at making this a synthetically useful protocol to compliment existing methodologies for the synthesis of sulfonamides[9–14] and hindered arylsulfonates.[15,16] Work in this regard will be reported in a future full paper.

Acknowledgements

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7. All compounds were fully characterized and gave spectroscopic data consistent with the structures.
8. *Typical procedure*. 2,6-Dimethylphenylcarbamate **14** (0.03 g, 0.18 mmol) was added portionwise to a suspension of 95% sodium hydride (0.012 g, 0.48 mmol) in dry THF (2 mL). Benzenesulfonyl chloride **1** (0.089 mL, 0.36 mmol) was added to the resulting mixture, which was then heated at 40–45 °C. The reaction was monitored by TLC (EtOAc–Hexane, 1:4) and upon completion (16 h), the mixture was concentrated under an air blast. The crude mixture was purified by preparative thin layer chromatography to afford benzenesulfonic acid 2,6-dimethylphenyl ester **36** (0.043 g, 90%) and benzenesulfonamide **4** (0.017 g, 61%).
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