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A new strategy for the chemoselective sulfonamide N-alkylation of sulfonyl ureas under neutral and mild conditions

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ABSTRACT

An efficient and chemoselective sulfonamide N-alkylation of sulfonyl ureas is described. The sulfonyl urea derivatives, prepared in situ by the addition of an amine to an arylsulfonyl isocyanate, are selectively alkylated in excellent yields under neutral and mild conditions by treatment with trialkylphosphite–dimethyl acetylenedicarboxylate at ambient temperature.

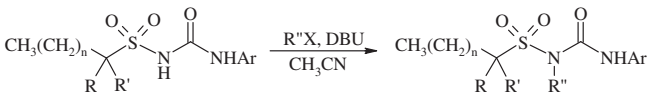
N-Alkylation is an important reaction in synthetic organic chemistry. The N-alkylation reaction with alkyl halides is well known,[1] but the use of alkyl halides is undesirable from an environmental point of view. Other alkylating reagents and conditions for N-alkylation include: alcohols/metal catalysts,[2] alcohols/Ph3P/DDQ,[3] highly active methylating reagents such as Me_2SO_4, Me_3PO_4, and Me_2CO_3,[4] and also reductive amination of carbonyl compounds.[5] However, most of these methods have disadvantages such as high reaction temperatures, long reaction times, use of strong reducing reagents or hydrogen gas, and in some cases, use of very hazardous reagents.

The sulfonyl urea unit is an important structural motif found in biologically active organic compounds. These compounds, first discovered by Janbon et al.,[6] have been shown to be highly active herbicides, antidiabetics, and antitumor agents.[7–12]

Chemoselectively alkylated sulfonyl ureas are important compounds in medicinal studies. An important procedure for acquiring these compounds was reported by Roth et al. in 1995 in which sulfonyl ureas were alkylated with alkyl halides in the presence of DBU in acetonitrile (Scheme 1).[13]

In this context, and as part of our continuing effort on the design of new routes for the preparation of biologically active organic compounds, herein, we report a new reagent for the chemoselective sulfonamide N-alkylation of sulfonyl ureas under neutral and mild conditions. Thus, a mixture of an amine 1 and an aryl sulfonyl isocyanate **2** was converted into the corresponding sulfonyl urea in dry CH_2Cl_2 at ambient temperature. The reactions reached completion within a few minutes, which was indicated by TLC monitoring. After addition of a trialkyl phosphite **3**, a solution of dimethyl acetylenedicarboxylate (DMAD) (**4**) in dry CH_2Cl_2 was slowly added to the reaction mixture and stirring was continued at ambient temperature for further two hours to afford the alkylated sulfonyl ureas **5a–q** in 85–98% yields (Scheme 2). TLC and ^1H NMR analysis of the reaction mixture clearly indicated the formation of the corresponding alkylated sulfonyl ureas **5**. Any product other than **5** or **6** could not be detected by NMR spectroscopy.

The structures of the isolated products **5** were deduced on the basis of IR, ^1H, and ^{13}C NMR spectroscopy and mass spectrometry. The mass spectrum of **5a** displayed the molecular ion (M++1) at $m/z = 333$, which was consistent with the ethylated 1:1 adduct of benzylamine and *p*-toluenesulfonyl isocyanate. The IR spectrum of **5a** showed absorptions at 3394 (w), 1691 (s), 1342 (s), and 1152 (s) cm^{-1} indicating the presence of NH, C=O, and S=O functional groups, respectively. The ^1H NMR spectrum of **5a** exhibited a



Scheme 1.

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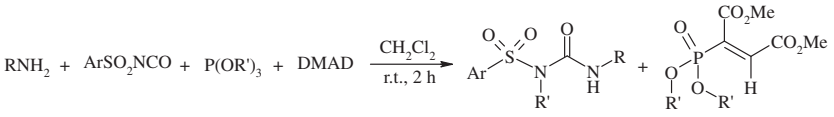
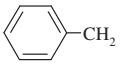
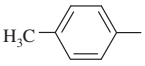
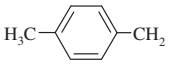
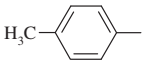
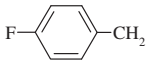
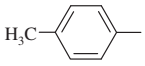
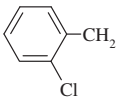
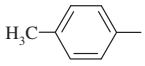
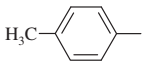
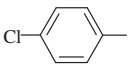
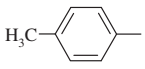
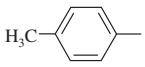
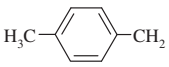
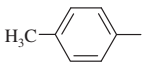
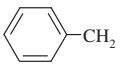
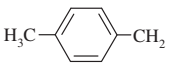
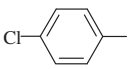
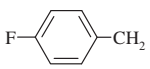
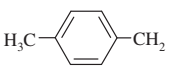
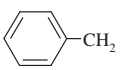
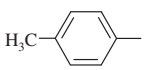
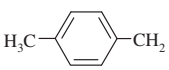
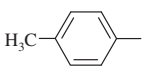
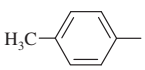
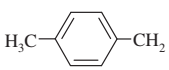


1 2 3 4 5 6

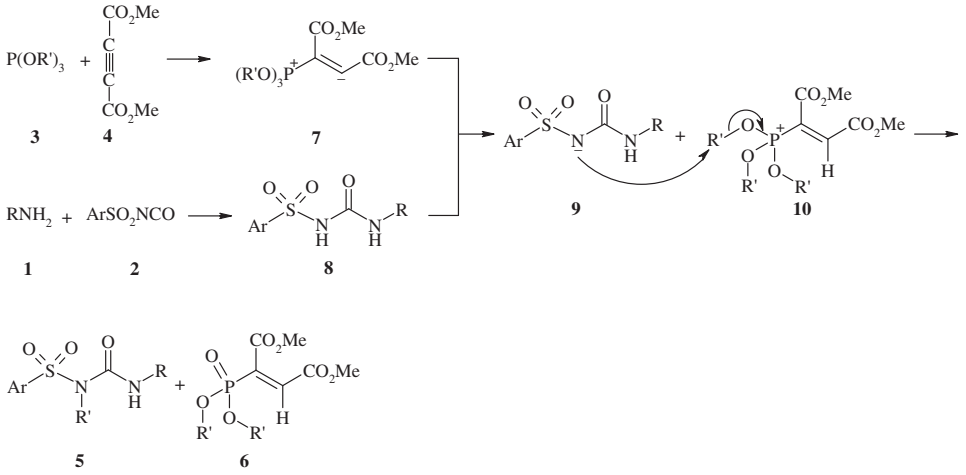
Product	R	Ar	R'	Yield of **5** (%)[a]
5a			Et	98
5b			Et	98
5c			Et	96
5d			Et	90
5e			Et	95
5f			Et	94
5g			Me	97
5h			Me	96
5i			Me	98
5j			Me	96
5k			Me	95
5l			Et	91
5m			Et	92
n			*i*-Pr	85
5o			*i*-Pr	86
5p			*n*-Bu	94
5q			*n*-Bu	92

[a] Isolated yield

Scheme 2.

sharp singlet at δ 2.39 due to the aryl methyl group along with characteristic resonances for the ethyl group (δ 1.24, t and 3.74, q; J = 7.0 Hz for both). Signals confirming the selective alkylation were seen as a doublet and a triplet for the mutually coupled methylene (at δ 4.44, J = 5.6 Hz) and the adjacent NH (δ 7.69, J = 5.6 Hz) groups. Characteristic signals for the nine protons of the two aryl substituents were observed with appropriate chemical shifts and coupling constants. The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed characteristic signals at δ 15.33 (CH_2CH_3), 21.55 (Ar-CH_3), and 41.72 and 44.94 (for the two CH_2 groups) along with further nine distinct resonances (5CH, 3C, and the urea carbonyl) in agreement with the proposed structure.[14]

A plausible mechanism for the formation of the alkylated sulfonyl ureas **5** is provided in Scheme 3. It is reasonable to assume that the zwitterionic intermediate **7**, formed by nucleophilic addition of the phosphite **3** to DMAD **4**,[15–20] is protonated by the in situ-prepared sulfonyl urea **8** from the reaction of the amine **1** and the arylsulfonyl isocyanate **2**. Next, the alkyl group of the vinyltrialkoxyphosphoni-



Scheme 3.

um ion **10** may be attacked by the conjugate base **9** of the NH-acid to afford the corresponding selectively alkylated sulfonyl urea **5**. Dimethyl (*E*)-2-(diethoxyphosphoryl)-2-butenedioate (**6**, R′ = ethyl) was isolated as a by-product and characterized. This further supports the possibility of the proposed mechanism.[21]

In conclusion, we have developed a simple and efficient strategy for the direct one-pot synthesis and chemoselective sulfonamide N-alkylation of sulfonyl ureas which are of potential synthetic and pharmacological interest. Excellent yields of the products, short reaction times, ambient temperature, and mild conditions are the main advantages of this method. The reactions were performed under neutral conditions, and the starting materials and reagents do not require any activation.

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14. *Typical procedure for the preparation of compounds 5a–q, exemplified with* **5a**: A solution of benzylamine (0.107 g, 1 mmol) and *p*-toluenesulfonyl isocyanate (0.197 g, 1 mmol) in dry CH_2Cl_2 (5 mL) was stirred at 25 °C for 5 min. Then triethylphosphite (0.166 g, 1 mmol) was added. Next, a solution of dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise over 10 min, and the resulting mixture was stirred at 25 °C for 2 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (Merck silica gel, 60 mesh) using *n*-hexane–EtOAc (4:1) as eluent. *{[(Benzylamino)carbonyl](ethyl)amino}(4-methylphenyl)dioxo-λ^6-sulfane* (**5a**): Yield: 0.32 g (98%); colorless crystals, mp 135–136 °C. IR (KBr) (ν_{max}/cm^{-1}): 3394 (NH), 1691 (C=O), 1597, 1520, 1342, 1242, 1152, 1087, 944, 812, 728, 699, 666. EI-MS, *m*/*z* (%): 333 (M^++1, 51), 290 (4), 177 (75), 155 (12), 106 (100), 91 (84), 77 (4), 65 (22). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.24 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.39 (s, 3H, CH_3), 3.74 (q, J = 7.0 Hz, 2H, CH_2CH_3), 4.44 (d, J = 5.6 Hz, 2H, $NHCH_2$), 7.20–7.33 (m, 7H, 7CH), 7.62 (d, J = 8.3 Hz, 2H, 2CH), 7.69 (t, J = 5.6 Hz, 1H, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.33 (CH_2CH_3), 21.55 (CH_3), 41.72 and 44.94 ($2CH_2$), 126.87, 127.49, 127.65, 128.68 and 130.00 (9CH), 136.40, 138.23 and 144.68 (3C), 152.51 (C=O).
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