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Substituted Sulfonamides via a Three Component Reaction on Solid Support

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Abstract

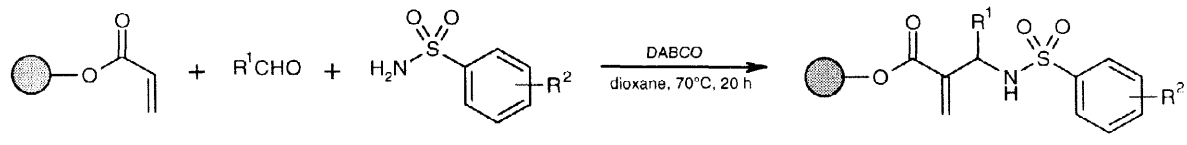
A new scaffold for combinatorial chemistry has been developed. In a three component reaction using polymer bound acrylic acid, aldehydes and sulfonamides under Baylis-Hillman reaction conditions, substituted 2-methylidene-3-aminoarylsulfonylpropionic acids were synthesised. After cleavage from the solid support, the products were obtained in high purities. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: *Baylis-Hillman reaction; Solid-phase synthesis; Combinatorial chemistry*

Combinatorial chemistry [1] provides efficient methods for the parallel synthesis of large numbers of small organic molecules for the drug discovery research. Structurally diverse collections for the high throughput screening can be synthesised in only a few steps. In particular, solid phase chemistry is less time consuming and can be more readily automated. Therefore, one of the important challenges remains the transfer of solution phase reactions to the solid phase and their often tedious optimization to allow the incorporation of a variety of structurally diverse building blocks.

After having worked out the Baylis-Hillman reaction [2] on solid supports [3], we focused our work on applications of the resulting allylic alcohols [4]. Another point of interest was to obtain a higher diversity in the Baylis-Hillman reaction. A three component solution phase synthesis of substituted sulfonamides by reaction of an acrylic ester, an aldehyde and toluenesulfonamide under Baylis-Hillman conditions was reported [5,6] The reaction is catalysed by DABCO [5] or PPh_3 [6].

In this paper we describe the first solid support version of this reaction to afford substituted sulfonamides via a Baylis-Hillman type reaction (**Scheme 1**). Acrylic acid attached on the 2-chlorotrityl chloride resin was reacted with 4-trifluoromethylbenzaldehyde and p-toluenesulfonamide in the three component reaction.



Scheme 1. Three component reaction on solid phase bound acrylic acid.

The best results were obtained using 16 eq. of 4-trifluoromethylbenzaldehyde, 20 eq. of

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toluenesulfonamide and 1,6 eq. of the catalyst DABCO in dioxane at 70 °C within 20 h.

In the following we applied these reaction conditions to different aldehydes (**Table 1**) and different sulfonamides (**Table 2**) [7]. The structures of all products were confirmed by ESI mass spectrometry, analytical HPLC and ^{1}H- and ^{13}C-nmr spectroscopy for some representative examples.

Table 1. Three component reaction using toluenesulfonamide, different aldehydes and polymer bound acrylic acid.

Pos.	Aldehyde	Purity[a] (%)
1	4-Fluorobenzaldehyde	69
2	4-Chlorobenzaldehyde	90
3	4-Bromobenzaldehyde	90
4	2-Furfural	60
5	2-Thiophenaldehyde	84
6	3-Trifluoromethylbenzaldehyde	86
7	2-Bromobenzaldehyde	82
8	3,4-Dichlorobenzaldehyde	72

[a] Purity determined by HPLC (λ = 214 nm).

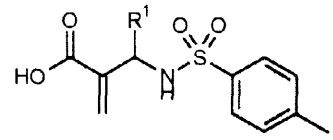
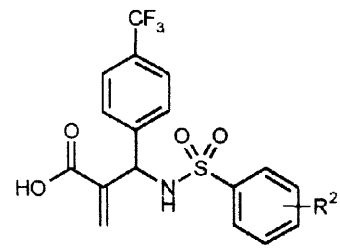


Table 2. Three component reaction by using 4-trifluoromethylbenzaldehyde, different sulfonamides and polymer bound acrylic acid.

Pos.	Sulfonamide	Purity[a] (%)
1	Toluenesulfonamide	83
2	Benzenesulfonamide	77
3	4-Nitrobenzenesulfonamide	53
4	2-Chlorobenzenesulfonamide	84
5	3-Chlorobenzenesulfonamide	71
6	4-Bromobenzenesulfonamide	73
7	4-Methoxybenzenesulfonamide	78
8	Dansylamide	88

[a] Purity determined by HPLC (λ = 214 nm).



In summary we have successfully developed a three component reaction under Baylis-Hillman conditions which yields substituted 2-methylidene-3-aminoarylsulfonylpropionic acids. They can be used as a scaffold for many applications, such as the alkylation or the Mitsunobu reaction but also for a transformation of the double bond. The optimization of these various reactions is currently in progress.

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References and Notes

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[7] Typical procedure: for the 3-component-reaction (Pos. 7, Table 2): 2-Chlorotrityl chloride PS (1% DVB) resin (50 mg, capacity: 1.3 mmol/g) was loaded with 4 eq. acrylic acid (18 µl) in 600 µl DMF/DCM (1:1) by using 6 eq. Et_3N (55 µl) for 4 h at 0 °C. After washing, the resin was suspended in 600 µl dioxane and 16 eq. 4-trifluoromethylbenzaldehyde (176 µl), 20 eq. 4-methoxyphenylsulfonamide (234 mg) and 1,6 eq. DABCO (14 mg) were added and stirred for 16 h at 70 °C. The resin was cleaved with 600 µl DCM/TFA (95:5) for 30 min. After concentration to dryness and lyophilization from $tBuOH/H_2O$ (4:1), the crude product was analysed by HPLC (λ = 214 nm): 78%, MS (ESI): $[M+H^+]$ = 414 and ^{1}H- and ^{13}C-NMR. ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.78 (s, 3), 5.37 (d, 2, J = 9.5 Hz), 5.90 (s, 1), 6.17 (s, 1), 6.94 (d, 2, J = 8.9 Hz), 7.29 (d, 2, J = 8.1 Hz), 7.54 (d, 2, J = 7.9 Hz), 7.57 (d, 2, J = 8.8 Hz), 8.46 (d,2,J = 9.6 Hz), 12.72 (s, 1). ^{13}C NMR (250 MHz, DMSO-d_6) δ 56.3, 66.9, 114.0, 122.0, 125.0, 125.8, 127.6, 128.0, 128.6, 132.7, 140.5, 144.3, 162.1, 166.3.