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Solid-phase synthesis of α-sulfonylamino amide derivatives based on Ugi-type condensation reaction using sulfonamides as amine input†

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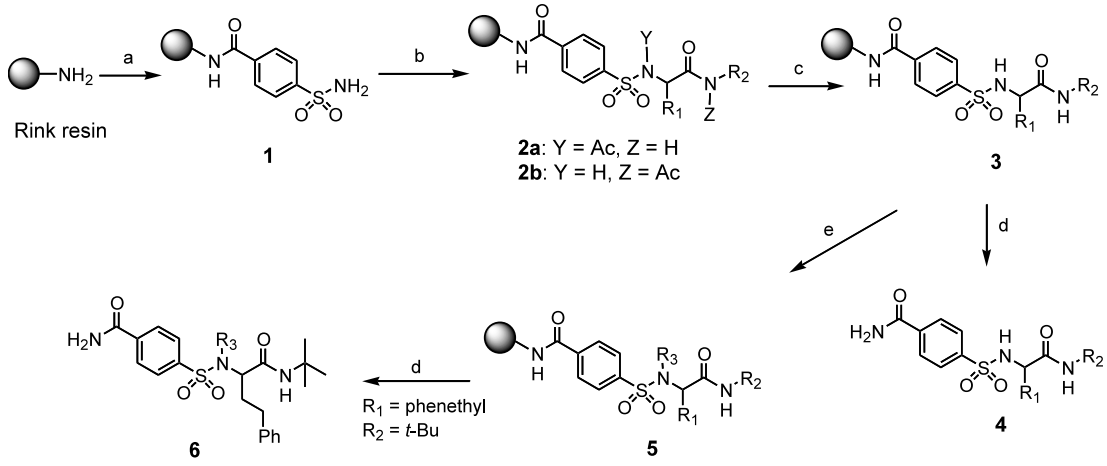
Abstract—A method for solid-phase synthesis of α-sulfonylamino amides has been developed, which relies on a new Ugi-type 4-component condensation reaction involving arylsulfonamides as an amine input followed by removal of the acid moiety under the basic conditions. Either polymer-bound sulfonamides or carboxylic acids can be used in this reaction to afford structurally diverse products with good purity and in moderate to excellent yield. © 2002 Elsevier Science Ltd. All rights reserved.

The importance of multi-component reactions (MCR) has received increasing attention due to the recent emergence of combinatorial chemistry technology.[1] These reactions enable to introduce three or more different building blocks, in most cases, in a single chemical step to give products with multiple diversity points. The Ugi condensation reaction employs four components including a carboxylic acid, an amine, an aldehyde and an isocyanide to construct an α-acylamino amide in one step, which can subsequently be converted into the corresponding amino acid, ester, lactam, lactone, etc.[2,3] The versatility of the reaction has also been demonstrated in the solid-phase syntheses of a variety of biologically interesting heterocyclic



Scheme 1. *Reagents and conditions:* (a) 4-carboxybenezenesulfonamide (6 equiv.), DIC (6 equiv.) and HOBt (6 equiv.), DCM/DMF, 2 h; (b) R_1CHO (10 equiv.), AcOH (10 equiv.), R_2NC (10 equiv.), MeOH/THF (1:1), 60°C, 24 h; (c) 40% aq. $MeNH_2$/THF (v/v, 1:1), rt, overnight; (d) 25% TFA in DCM, rt, 30 min; (e) R_3OH (10 equiv.), PPh_3 (10 equiv.), DIAD (10 equiv.), THF, rt, 2 h.

Keywords: solid-phase synthesis; multi-component condensation reaction; sulfonamide.

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structures via post-Ugi transformations.[4] Our interest in broadening the scope of the known reaction and developing efficient methods for parallel synthesis of structurally diverse α-sulfonylamino amide derivatives[5] prompted us to investigate the condensation reaction in the presence of sulfonamides instead of amines.

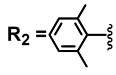
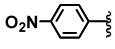
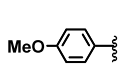
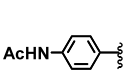
The reactivity of the sulfonamides towards the Ugi-type condensation was initially examined in solution phase. *p*-Toluenesulfonamide was treated with HOAc (1 equiv.), hydrocinnamaldehyde (1 equiv.) and *t*-butyl isocyanide (1 equiv.) in THF and MeOH (v/v, 1:1) for 3 days to give a complex mixture with a majority of the unreacted sulfonamide and a trace amount of the desired four-component condensation product. This result encouraged us to attempt the solid-phase approach.

As shown in Scheme 1, resin-bound benzenesulfonamide **1** was prepared by coupling 4-carboxybenzenesulfonamide onto Rink resin[6] by using the DIC/HOBt coupling protocol. Subsequently, it was treated with HOAc (10 equiv.), hydrocinnamaldehyde (10 equiv.) and *t*-butyl isocyanide (10 equiv.) in the same solvent system (THF/MeOH, 1:1) at rt for 3 days. The formation of the desired product was unambiguously confirmed by LC–MS analysis upon cleavage with 20% TFA in DCM, however, most of the starting sulfonamide was recovered. The reaction was then examined at 60°C for 24 h to give a mixture of the expected Ugi-products, *N*-acetyl α-sulfonylamino amides (**2a** and/or **2b**), and a small amount of deacetylated product **3**. The acetyl moiety on the products **2a** and/or **2b** was readily removed by treating the resin with a 1:1 mixture of 40% aq. $MeNH_2$ and THF, leading to the complete conversion into the resin-bound sulfonamides **3**. The corresponding α-sulfonylamino amides **4** were obtained upon cleavage from the resin by the standard TFA treatment.

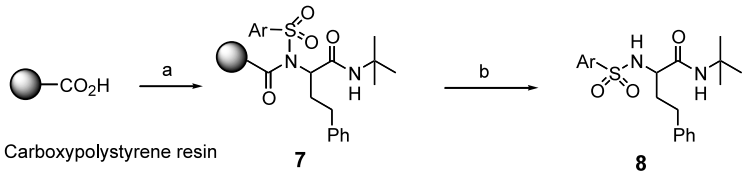
The above condition was found to be applicable for a broad range of aldehydes and isocyanides as illustrated in Table 1 (**4a**–**j**,[7] entries 1–10). More importantly, the diversity of the products was further expanded by *N*-alkylation of **3** with various alcohols under the Mitsunobu conditions to afford *N*-alkylated products **5** which were then cleaved by TFA to give the products **6** in good yield as exemplified by **6a**–**c**[8] in Table 1 (entries 11–13).

An alternative approach was examined with a polymer-bound carboxylic acid in this new condensation reaction. Carboxypolystyrene[6] was treated with various arylsulfonamides in the presence of hydrocinnamalde-

Table 1.

Entry		Product	Purity[c]	Yield	Entry		Product	Purity[c]	Yield
1	4a	R_1 = Ph, R_2 = 	90%	89%[b]	10	4j	R_1 = Ph, R_2 = 	70%	87%[a]
2	4b	R_1 =  , R_2 = 	95%	>95%[a]	11	6a	R_3 = Me	85%	82%[b]
3	4c	R_1 = MeO-  , R_2 = 	90%	>95%[a]	12	6b	R_3 = Ph-O-	85%	83%[b]
4	4d	R_1 =  , R_2 = 	60%[d]	>90%[a] (63%[b])	13	6c	R_3 = Ph 	60%	77%[a]
5	4e	R_1 = CF_3-  , R_2 = 	90%	94%[b]	14	8a	Ar = 	65%	52%[b]
6	4f	R_1 = F-  , R_2 = 	95%	90%[b]	15	8b	Ar = O_2N- 	75%	87%[b]
7	4g	R_1 =  , R_2 =	95%	90%[b]	16	8c	Ar = 	75%	93%[b]
8	4h	R_1 = Ph , R_2 = 	75%	60%[b]	17	8d	Ar = MeO- 	80%	90%[b]
9	4i	R_1 = Ph , R_2 = Ph	60%	40%[b]	18	8e	Ar = AcHN- 	85%	80%[b]

[a] determined by weight of the crude products based on the loading of the resins. [b] isolated yields. [c] deterimined by LC-MS using both UV and ELS detectors; further confirmed by ^{1}HNMR analysis. [d] a significant amount of unreacted sulfonamide recovered.



Scheme 2. *Reagents and conditions:* (a) hydrocinnamaldehyde (10 equiv.), arylsulfonamide (10 equiv.) and *t*-butyl isocyanide (10 equiv.), THF/MeOH, 60°C, 24 h; (b) 40% aq. $MeNH_2$/THF (v/v, 1:1), rt, overnight.

hyde and *t*-butyl isocyanide at 60°C for 24 h in the same solvent system (THF/MeOH) as illustrated in Scheme 2. A traceless cleavage strategy was applied by treating the resin **7** with $MeNH_2$ in H_2O/THF to release the desired α-sulfonylamino amide derivatives **8** which are structurally complementary to the products obtained from the first approach described in Scheme 1. A set of representative examples is shown in Table 1 (**8a**–**e**,[9] entries 14–18).

In conclusion, an efficient method for the solid-phase construction of α-sulfonylamino amides has been developed by utilizing arylsulfonamides instead of amines in the Ugi four-component condensation reaction. These two approaches, utilizing polymer-bound arylsulfonamides and carboxylic acids, allow a quick access to the corresponding compound libraries with a high degree of structural diversity. The further chemical manipulation leading to other biologically important core structures is under investigation.

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7. General procedures for the preparation of compounds **4a**–**j**:
   Aminosulfonylbenzamide Rink resin **1** (1 g, 0.5 mmol /g) in a 40 mL vial was swelled with 2.5 mL of THF. To this mixture were then added solutions of 1 M hydrocinnamaldehyde in MeOH (5 mL, 10 equiv.), 1 M AcOH in THF (5 mL, 10 equiv.) and 2 M *t*-butyl isocyanide in MeOH (2.5 mL, 10 equiv.). The suspension was mixed on an ACT Labmate[6] at 60°C for 24 h. The resin was filtered, washed with DMF (3×), MeOH (3×) and DCM (3×). After drying, the resin was treated with a mixture of 40% aq. $MeNH_2$ and THF (10 mL, 1:1) at rt overnight. The resin was filtered, washed as usual and dried in vacuo (1.15 g). The dried resin **3a** (115 mg) was treated with 25% TFA in DCM for 30 min. The cleavage solution was evaporated to give a residue which was re-dissolved in acetonitrile. The solvent was then removed on a rotavapor to give the crude product (25.4 mg), which was purified by preparative TLC to give the pure product (18.6 mg, 89% yield). ^{1}H NMR (CD_3OD): **4a**: δ 7.94–8.11 (m, 4H), 7.10–7.32 (m, 5H), 3.78–3.85 (m, 1H), 2.73 (m, 1H), 2.61 (m, 1H), 1.94 (m, 1H), 1.86 (m, 1H), 1.15 (s, 9H). **4h**: δ 8.00 (d, J=8.5 Hz, 2H), 7.86 (d, J=8.5 Hz, 2H), 7.09–7.24 (m, 5H), 3.75–3.77 (dd, 1H), 3.28 (m, 1H), 2.63–2.68 (m, 1H), 2.49–2.55 (m, 1H), 0.90–1.90 (m, 12H). **4i**: 7.98 (d, J=8 Hz, 2H), 7.91 (d, J=8 Hz, 2H), 7.03–7.27 (m, 10H), 4.16 (d, J=12 Hz, 1H), 4.10 (d, J=12 Hz, 1H), 3.81 (m, 1H), 1.35 (m, 2H), 0.92 (m, 2H).
8. General procedures for the preparation of compounds **6a**–**c**:
   To the above resin-bound product **3a** (200 mg, ~0.087 mmol) placed in an 8 mL vial, were added solutions of 2 M methanol in THF (10 equiv.), 1 M triphenylphosphine in THF (10 equiv.) and 1 M DIAD in THF (10 equiv.). The suspension was mixed on an ACT Labmate at rt for 5 h. The resin was filtered, washed as usual and dried. The obtained resin was treated with 25% TFA in DCM for 30 minutes. The cleavage solution was evaporated to give a residue which was re-dissolved in acetonitrile. The solvent was then removed on a rotavapor to give the crude

product **6a** (85% purity), which was purified by preparative TLC to give the pure product (30.7 mg, 82% yield). ^{1}H NMR (CD_3OD): δ 8.04 (d, $J=7$ Hz, 2H), 7.89 (d, $J=7$ Hz, 2H), 7.11–7.38 (m, 5H), 4.38 (t, 1H), 3.00 (s, 3H), 2.50 (t, 2H), 1.97–2.01 (m, 1H), 1.70–1.74 (m, 1H), 1.21 (s, 9H). **6b**: δ 8.00 (d, $J=8$ Hz, 2H), 7.88 (d, $J=8$ Hz, 2H), 6.99–7.32 (m, 10H), 4.45–4.53 (dd, $J=11.50$ Hz, 2H), 4.21–4.24 (m, 1H), 3.80 (m, 1H), 3.68 (m, 2H), 3.53–3.56 (m, 1H), 1H), 2.46 (m, 2H), 2.06 (m, 1H), 1.68 (m, 1H), 1.21 (s, 9H).

9. General procedures for the preparation of compounds **8a**–**e**: To carboxypolystyrene resin (100 mg, 1 mmol/g) were added solutions of 1 M benzenesulfonamide in THF (1 mL, 10 equiv.), 2 M hydrocinnamaldehyde in MeOH (0.5 mL, 10 equiv.) and 2 M *t*-butyl isocyanide in MeOH (0.5 mL, 10 equiv.). The suspension was mixed on an ACT Labmate at 60°C for 24 h. The resin was filtered, washed as usual and dried. The resin was then treated with a mixture of 40% aqueous methylamine and THF (1:1, 2 mL) at rt for 12 h. The resin was filtered and rinsed with THF (4 mL). The combined filtrates were concentrated to give the crude product **8a** (65% purity), which was purified by preparative TLC to give the pure product (19.4 mg, 52% yield). ^{1}H NMR (CD_3OD): δ 7.53–7.87 (m, 5H), 7.08–7.24 (m, 5H), 3.74 (t, 1H), 2.64 (m, 1H), 2.48 (m, 1H), 1.86 (m, 1H), 1.75 (m, 1H), 1.14 (s, 9H). **8b**: δ 8.35–7.13 (m, 9H), 3.894 (m, 1H), 2.64 (m, 1H), 2.69 (t, 2H), 2.01 (m, 1H), 1.82 (m, 1H), 1.75 (m, 1H), 1.36 (s, 9H). **8c**: δ 8.08 (d, $J=8$ Hz, 1H), 7.91 (d, $J=8$ Hz, 1H), 7.74–7.83 (m, 2H), 7.13–7.25 (m, 5H), 3.92 (m, 1H), 2.71 (m, 1H), 2.58 (m, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.11 (s, 9H).