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# N-Arylation of Sulfonamides on Solid Supports

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# N-Arylation of Sulfonamides on Solid Supports

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A general and mild method for the N-arylation of sulfonamides on solid supports is reported. Copper acetate, triethylamine mediated coupling of arylboronic acids at room temperature to solid-supported sulfonamides gave good to excellent yields of the desired N-arylsulfonamides. Sulfonamide bond cleavage of the *o,p*-dinitrobenzene(N-aryl)sulfonamide provides a route to N-arylated secondary amine products.

## Introduction

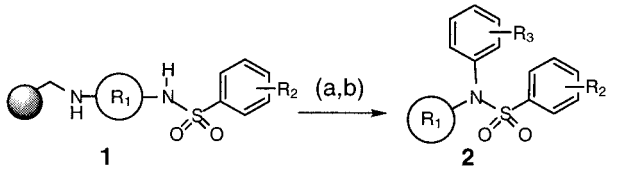
Reliable synthetic methods for the substitution of solid-supported amines provide valuable tools for the synthesis of diverse compound libraries. Acylation (amide, carbamate, urea, and sulfonamide formation) and alkylation (alkyl halide, Mitsunobu, and reductive amination) of solid-supported amines have been optimized and utilized in a large number of multistep solid-phase syntheses.[1] Interestingly, a general method for the N-arylation of solid-supported amines has not been demonstrated to date. N-arylation reactions of amines on solid supports have been limited to suitably activated aromatic heterocyclic halides[2] and ortho-halonitrobenzene derivatives.[3] We report herein the application of the copper acetate promoted C/N cross-coupling reaction to solid-supported sulfonamides **1** to afford N-arylsulfonamides **2** (Scheme 1). A systematic optimization of reaction conditions along with investigations into the steric and electronic influences of the sulfonamide and arylboronic acid were investigated. Further elaboration of the arylated amine is demonstrated by cleavage of the *o,p*-dinitroarylsulfonamide to give N-arylated secondary amines which can be acylated.

## Results and Discussion

Chang et al.[4] initially reported the copper acetate promoted C/N cross-coupling reaction of a variety of compounds bearing a free N−H. We have recently published our studies of the N-arylation of heterocycles in solution[5] and on solid supports[6] using this methodology. We describe herein our efforts toward N-arylation of amides, carbamates, ureas, and sulfonamides on solid supports. Of these, we found the sulfonamides gave the only detectable products when subjected to the literature reaction conditions (Scheme 2). Our negative results for amides and carbamates are consistent with the reactivity of similar substrates in solution, though the N-arylation of the solid-supported ureas in Scheme 2 was expected to proceed as demonstrated by the N-arylation of analogous ureas in solution. Further investigations into the reactivity of other ureas are ongoing.

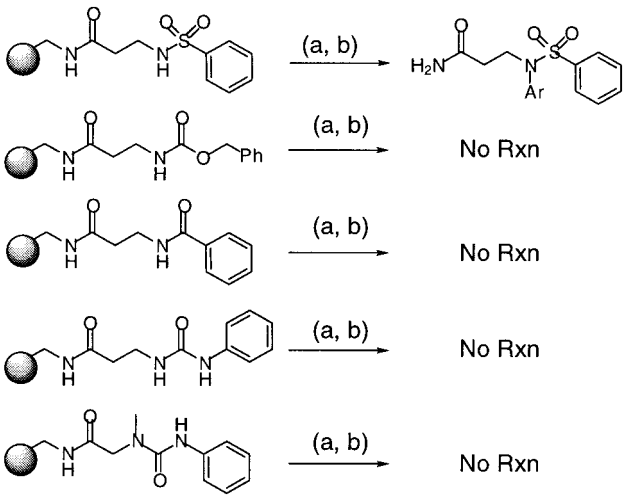
A variety of reaction conditions were performed to optimize the N-arylation of sulfonamides on solid supports (Table 1). We found that similar conditions for solution-phase N-arylation reactions provided the desired N-arylsulfonamides in moderate yields.[4] Reaction of the solid-supported sulfonamide **3** with 4 equiv of boronic acid, 2 equiv of $Cu(OAc)_2$, and 4 equiv of TEA or DIEA in THF in the presence of 4 Å powdered molecular sieves gave optimal yields of the N-arylated sulfonamide **4**. Slightly lower yields were observed when the solvent was changed to DCM, which is likely due to the limited solubility of $Cu(OAc)_2$ and the boronic acid. Significantly lower yields were observed when pyridine was used as the base or molecular sieves were not used. Powdered molecular sieves gave substantially higher yields compared to sieve pellets and could be easily removed by filtration since the pore size of the standard frit was larger than the sieve particle size. After one coupling for 24 h under

**Scheme 1**[a]




[a] Reagents and conditions: (a) $Cu(OAc)_2$, $PhB(OH)_2$, TEA, THF, 4 Å sieves; (b) TFA−DCM (1:1).

**Scheme 2**[a]




[a] Reagents and conditions: (a) $Cu(OAc)_2$ (2 equiv), 4-$MePhB(OH)_2$ (4 equiv), TEA (4 equiv), THF, 4 Å sieves, repeat 2×; (b) TFA−DCM (1:1).

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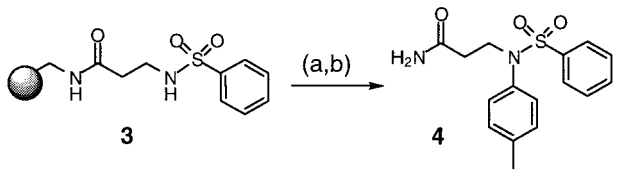
**Table 1.** N-Arylation Reaction Optimization




(a) $Cu(OAc)_2$ (2 equiv), 4-$MePhB(OH)_2$ (4 equiv), solvent, base (4 equiv), 4 Å sieves, repeat 2×; (b) TFA−DCM (1:1)

| entry | base | solvent | sieves[a] | purity[b] (%) |
|---|---|---|---|---|
| 1 | TEA | THF | yes | 100 |
| 2 | DIEA | THF | yes | 96 |
| 3 | TEA | DCM | yes | 83 |
| 4 | Pyr | THF | yes | 24 |
| 5 | Pyr | DCM | yes | 35 |
| 6 | TEA | THF | no | 33 |

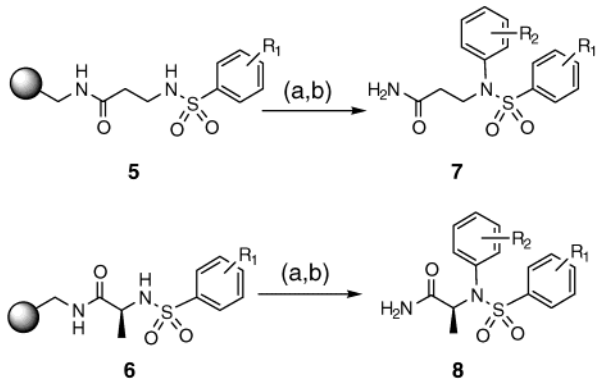
[a] Powdered 4 Å molecular sieves from Aldrich. [b] HPLC peak area, starting material only other product present in HPLC (220 and 254 nm).

the optimized conditions, these reactions were typically ∼75% complete, though the only other species present in the cleaved material was the starting sulfonamide. Kinetic studies showed that the reaction was ∼50% complete after just 3 h, but had stopped after 24 h. In an attempt to drive these reactions to completion and limit the reaction time to a single overnight run, two 3 h couplings were performed followed by one overnight coupling. TFA cleavage of the products, followed by resin trapping of undesired copper salts with Chelex resin[7] gave excellent conversions (65−100%) to the N-arylated sulfonamides in good isolated yields (43−81%).

A series of sulfonamides were synthesized on solid supports to study the steric effects of the amine and boronic acid as well as electronic effects of the sulfonamide during the C/N cross-coupling reaction (Table 2). In general, we found no significant electronic effects caused by electron-donating or electron-withdrawing groups on the aryl ring of the phenylsulfonamide, though yields were variable. These results demonstrate that the acidity of the sulfonamide NH is not critical to the success of the N-arylation reaction. The steric effects of α-substitution of the solid-supported alanine derivative **6** compared to the unsubstituted *β*-alanine derivative **5** gave comparable yields of the N-arylated sulfonamides (**8** and **7**, respectively). Overall, these results demonstrate that α-substitution to the amine is tolerated. The most significant limitations discovered to date are the low yields obtained when *o*-methylarylboronic acid is used in these reactions (**7f**, 43%; **8f**, 0%). Presumably, the ortho substitution of the boronic acid sterically interferes with the approach of the metalated arene to the sulfonamide NH, especially when the amine is α-substituted (**8f**, 0%). Racemization under these conditions was investigated for compound **8e** and its D-isomer. Chiral reverse-phase HPLC provided baseline resolution of these two enantiomers and demonstrated that no racemizaton occurs during these N-arylation reaction conditions or upon cleavage from the resin.

Fukuyama's *o*,*p*-dinitroarylsulfonamides are versatile intermediates for solid-phase synthesis. N-Alkylation of the amine and subsequent cleavage of the sulfonamide with butylamine to afford secondary amines has been reported.[8]

**Table 2.** Electronic and Steric Effects on the N-Arylation of Sulfonamides

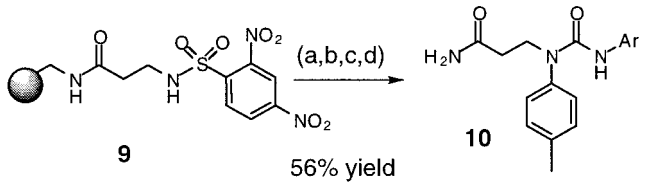



(a) $Cu(OAc)_2$ (2 equiv), 4-$MePhB(OH)_2$ (4 equiv), solvent, base (4 equiv), 4 Å sieves, repeat 2×; (b) TFA−DCM (1:1)

| product | $R_1$ | $R_2$ | conversion[a] | yield[b] (%) |
|---|---|---|---|---|
| **7a** | H | *p*-$CH_3$ | 77 | 63 |
| **8a** | H | *p*-$CH_3$ | 84 | 73 |
| **7b** | *p*-OMe | *p*-$CH_3$ | 83 | 52 |
| **8b** | *p*-OMe | *p*-$CH_3$ | 96 | 81 |
| **7c** | *p*-Br | *p*-$CH_3$ | 84 | 66 |
| **8c** | *p*-Br | *p*-$CH_3$ | 82 | 69 |
| **7d** | *p*-$NO_2$ | *p*-$CH_3$ | 100 | 77 |
| **8d** | *p*-$NO_2$ | *p*-$CH_3$ | 65 | 43 |
| **7e** | *m*-$CF_3$ | *p*-$CH_3$ | 100 | 77 |
| **8e** | *m*-$CF_3$ | *p*-$CH_3$ | 66 | 57 |
| **7f** | *m*-$CF_3$ | *o*-$CH_3$ | 68 | 48 |
| **8f** | *m*-$CF_3$ | *o*-$CH_3$ | 0 | 0 |

[a] Conversion to product based on HPLC peak area at 220 nm, starting material only other product present in HPLC (220 and 254 nm). [b] Purified yields based on initial loading (0.33 mmol/g) of Pal-resin.

**Scheme 3**[a]




[a] Reagents and conditions: (a) $Cu(OAc)_2$ (2 equiv), 4-$MePHB(OH)_2$ (4 equiv), TEA (4 equiv), THF, 4 Å sieves, repeat 2×; (b) 1 M butylamine/DCM; (c) phenylisocyanate, DCM; (d) TFA−DCM (1:1).

We have now demonstrated that *o*,*p*-dinitroarylsulfonamides **9** can be N-arylated utilizing boronic acids in the presence of copper acetate and a nitrogenous base (Scheme 3). The N-arylsulfonamide undergoes similar sulfonamide cleavage to give the N-aryl secondary amine which can be further elaborated, as demonstrated in urea **10**. This methodology for the synthesis of N-arylated amine derivatives on solid supports is complimentary to the previously reported palladium mediated couplings of amines to solid-supported aryl halides.[9] In these studies, the arylating agent (aryl halide) is solid-supported while the amine is used in vast excess in the presence of strong base at elevated temperatures (80−100 °C) overnight. The copper acetate promoted N-arylating reaction offers much milder conditions occurring at room temperature in the presence of a tertiary nitrogenous base.

## Conclusions

In summary, we have optimized conditions for the N-arylation of solid-supported sulfonamides using the copper

acetate mediated N/C cross-coupling of boronic acids. Reactions occur at ambient temperature in the presence of mild base, though they require multiple couplings under anhydrous conditions. The *o*,*p*-dinitroarylsulfonamides have been shown to be suitable substrates for the copper acetate mediated coupling of boronic acids, and the sulfonamide bond can be subsequently cleaved under very mild conditions. This procedure provides a selective method for the N-arylation of amines on solid supports. Application of this reaction to the synthesis of other N-arylated products is currently being pursued and will be reported in due course.

## Experimental Section

Fmoc-Pal resin (100−200 mesh, 1% cross-linked; loading of 0.4 mmol/g), PyBop, and Fmoc-protected amino acids were purchased from Advanced ChemTech. Sulfonyl chlorides, boronic acids, and powdered molecular sieves were purchased from Aldrich. Fmoc-Pal-PEG-PS resin (100−200 mesh; loading of 0.42 mmol/g) was purchased from PerSeptive Biosystem GmbH. Reactions were performed in bottom-and-top capped polypropylene-fitted tubes manufactured by Mitchell's Plastics. Reactions in the polypropylene tubes were shaken using Labquake Tube Rotor/Rocker manufactured by Thermolyne. $^1$H NMR spectra were recorded on a 500 MHz spectrometer using a flow injection probe. The chemical shifts are reported in ppm relative to TMS in a mixed solvent system of 75% DMSO-$d_6$/25% $CDCl_3$. High-resolution mass spectra were recorded using electrospray ionization. HPLC analyses were performed on a Hewlett-Packard 1090 liquid chromatography system using a photodiode array detector and ODS-A 5 mm (C18, 4.5 mm × 50 mm) YMC slimbore column with a gradient of 0% acetonitrile/water containing 0.1% TFA to 100% acetonitrile over 8 min at 3 mL/min flow rate. Peak areas were integrated at 220 and 254 nm. TLC analysis: silica gel, chloroform−methanol (9:1).

**Typical Procedure for the Preparation of Sulfonamides.** Fmoc-Pal resin (100−200 mesh, 2.0 g, loading of 0.4 mmol/g) was treated with 20% piperidine/DMF. After 30 min, the resin was washed with DMF (3×), MeOH (3×), and DCM (5×) and dried in vacuo. Commercially available Fmoc-$\beta$-Ala-OH and Fmoc-Ala-OH (5 equiv) were attached to Pal resin using PyBop (5 equiv) and DIPEA (5 equiv) in NMP (12 mL) at room temperature. After 2 h, the Kaiser test showed no free amino groups on the resin. The resin was washed thoroughly with NMP (3×), MeOH (3×), THF (3×), and DCM (5×). The amount of coupled Fmoc protected amino acid was measured by spectroscopic analysis of the Fmoc chromophore. Typical loading of the resin was 0.33 mmol/g. Fmoc deprotection of the resin was accomplished with 20% piperidine in DMF (30 min), followed by washing with DMF (3×), MeOH (3×), and DCM (5×). The resulting primary amine was treated with 5 equiv of the appropriate sulfonyl chloride and 5 equiv of triethylamine or pyridine in DCM for 2−4 h at room temperature. The resin was washed with DCM (3×), MeOH (3×), and DCM (5×) and dried in vacuo.

**N-Arylation of Sulfonamides (7a−7f, 8a−8f).** Sulfonamide resin (0.150 g, loading 0.33 mmol/g) was swelled in dry THF (0.3 mL) and the following reagents were added in a sequential fashion: boronic acid (4 equiv), anhydrous copper acetate (2 equiv), 4 Å powdered molecular sieves (0.1 g), triethylamine (2 equiv) and dry THF (1.0 mL). The heterogeneous mixture was mixed for 3 h. The resin was filtered off and washed alternately with THF (5×), DCM (5×), followed by THF (5×) and charged with fresh reagents. The reaction mixture was again mixed for 3 h. The washing procedure was repeated, and the resin was charged again with fresh reagents and then shaken overnight. The washing procedure was repeated as above. The product was cleaved from the solid support by treatment with 50% TFA in DCM for 1 h. The resin was filtered off and washed with DCM. The combined filtrates were evaporated to dryness. The light green residue was redissolved in THF and passed through Chelex 100 resin (Bio-Rad) to remove the trace of copper salts to provide colorless solid after solvent removal. Percent conversions are based on the HPLC analysis at 220 nm of this crude material. $^1$H NMR integration gave similar ratios for selected reactions. Isolated yields are given after purification by preparative TLC ($CHCl_3$/MeOH 9:1).

The following compounds were prepared according to the procedure described above.

**7a**: 77% conversion; 63% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 7.60 (m, 1H, Ar), 7.51 (m, 5H, Ar), 7.21 (bs, 1H, CONH), 7.07 (d, 2H, Ar), 6.81 (d, 2H, Ar), 6.73 (bs, 1H, CONH), 3.66 (m, 2H, $CH_2$), 2.25 (s, 3H, $CH_3$), 2.14 (m, 2H, $CH_2$); HRMS *m*/*e* calcd for $C_{16}H_{18}N_2O_3S$ Na $[M + Na]^+$ 341.0935, found 341.0942.

**7b**: 83% conversion; 52% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 7.41 (d, 2H, Ar), 7.20 (bs, 1H, CONH), 7.07 (d, 2H, Ar), 6.99 (d, 2H, Ar), 6.82 (d, 2H, Ar), 6.72 (bs, 1H, CONH), 3.80 (s, 3H, $OCH_3$), 3.61 (m, 2H, $CH_2$), 2.25 (s, 3H, $CH_3$), 2.12 (m, 2H, $CH_2$); HRMS *m*/*e* calcd for $C_{17}H_{20}N_2O_4SNa$ $[M + Na]^+$ 371.1044, found 371.1022.

**7c**: 84% conversion; 66% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 7.69 (d, 2H, Ar), 7.41 (d, 2H, Ar), 7.21 (bs, 1H, CONH), 7.09 (d, 2H, Ar), 6.85 (d, 2H, Ar), 6.74 (bs, 1H, CONH), 3.66 (m, 2H, $CH_2$), 2.26 (s, 3H, $CH_3$), 2.15 (m, 2H, $CH_2$), HRMS *m*/*e* calcd for $C_{16}H_{18}N_2O_3SBr$ $[M + H]^+$ 397.0221, found 397.0223.

**7d**: 100% conversion; 77% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 8.31 (d, 2H, Ar), 7.77 (d, 2H, Ar), 7.23 (bs, 1H, CONH), 7.10 (d, 2H, Ar), 6.87 (d, 2H, Ar), 6.75 (bs, 1H, CONH), 3.73 (m, 2H, $CH_2$), 2.27 (s, 3H, $CH_3$), 2.17 (m, 2H, $CH_2$); HRMS *m*/*e* calcd for $C_{16}H_{18}N_3O_5S$ $[M + H]^+$ 369.0967, found 364.0934.

**7e**: 100% conversion; 77% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 7.97 (m, 1H, Ar), 7.83−7.78 (m, 2H, Ar), 7.61 (m, 1H, Ar), 7.23 (s, 1H, CONH), 7.09 (d, 2H, Ar), 6.82 (d, 2H, Ar), 6.74 (s, 1H, CONH), 3.69 (m, 2H, $CH_2$), 2.26 (s, 3H, $CH_3$), 2.16 (m, 2H, $CH_2$); HRMS *m*/*e* calcd for $C_{17}H_{18}N_2O_3F_3S$ $[M + H]^+$ 387.0990, found 387.0975.

**7f**: 68% conversion; 48% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 8.15 (d, 1H, Ar), 8.00 (d, 1H, Ar), 7.92 (t, 1H, Ar), 7.75 (s, 1H, Ar), 7.32 (d, 1H, Ar), 7.27 (bs, 1H, CONH), 7.25 (m, 1H, Ar), 7.10 (t, 1H, Ar), 6.80 (bs,

1H, CONH), 6.60 (d, 1H, Ar), 3.97 (m, 1H, $CH_2$), 3.44 (m, 1H, $CH_2$), 2.25 (m, 1H, $CH_2$), 2.22 (s, 3H, $CH_3$), 2.16 (m, 1H, $CH_2$); HRMS *m*/*e* calcd for $C_{17}H_{18}N_2O_3SF_3$ $[M + H]^+$ 387.0990, found 387.0987

**8a**: 84% conversion; 73% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 7.62 (m, 2H, Ar), 7.57 (m, 1H, Ar), 7.47 (m, 2H, Ar), 7.25 (bs, 1H, CONH), 7.03 (m, 4H, Ar); 7.02 (bs, 1H, CONH), 4.77 (m, 1H, CH), 2.24 (s, 3H, $CH_3$), 0.96 (d, 3H, $CH_3$); HRMS *m*/*e* calcd for $C_{16}H_{19}N_2O_3S$ $[M + H]^+$ 319.1116, found 319.1067.

**8b**: 96% conversion; 81% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 7.55 (d, 2H, Ar), 7.23 (bs, 1H, CONH), 6.98 (m, 4H, Ar), 6.95 (bs, 1H, CONH), 6.80 (d, 2H, Ar), 4.73 (m, 1H, CH), 3.84 (s, 3H, $OCH_3$), 2.24 (s, 3H, $CH_3$), 0.95 (d, 3H, $CH_3$); HRMS *m*/*e* calcd for $C_{17}H_{21}N_2O_4S$ $[M + H]^+$ 349.1222, found 349.1197.

**8c**: 82% conversion; 69% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 7.65 (d, 2H, Ar), 7.51 (d, 2H, Ar), 7.36 (s, 1H, CONH), 7.07 (m, 4H, Ar), 7.03 (bs, 1H, CONH), 4.77 (m, 1H, CH), 2.25 (s, 3H, $CH_3$), 0.98 (d, 3H, $CH_3$), HRMS *m*/*e* calcd for $C_{16}H_{18}N_2O_3SBr$ $[M + H]^+$ 397.0221, found 397.0216.

**8d**: 65% conversion; 43% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 8.28 (d, 2H, Ar), 7.81 (d, 2H, Ar), 7.36 (s, 1H, CONH), 7.10 (m, 4H, Ar), 7.05 (bs, 1H, CONH), 4.82 (m, 1H, CH), 2.26 (s, 3H, $CH_3$), 1.00 (d, 3H, $CH_3$); HRMS *m*/*e* calcd for $C_{17}H_{18}N_2O_3F_3S$ $[M + H]^+$ 387.0990, found 387.1017.

**8e**: 66% conversion; 57% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 7.90 (m, 1H, Ar), 7.82 (m, 2H, Ar), 7,69 (m, 1H, Ar), 7.36 (bs, 1H, CONH), 7.10 (bs, 1H, CONH), 7.02 (m, 4H, Ar), 4.85 (m, 1H, CH), 2.25 (s, 3H, $CH_3$), 1.01 (d, 3H, $CH_3$); HRMS *m*/*e* calcd for $C_{17}H_{18}N_2O_3F_3S$ $[M + H]^+$ 387.0990, found 387.1017.

**Conversion of 9 to 10.** Compound **9** was synthesized and N-arylated (96% conversion to the N-arylated product) as described above. The deprotection of N-arylated 2,4-dinitrobenzenesulfonamide was achieved by treatment of the resin with 1 M *n*-butylamine in DCM at room temperature for 40 min. The resin was filtered off and washed alternately with DCM, MeOH, followed by DCM (5×). Phenylisocyanate (5 equiv) in DCM was added to the resin, and the reaction was mixed for 5 h. The chloranil test[10] showed that there was no free secondary amine left on the resin. The urea resin was washed with DCM, THF, MeOH, and DCM (5×) and treated with 50% TFA in DCM for 1 h. The resin was filtered off and washed with DCM. The combined filtrates were concentrated to give the desired urea **10** in 77% crude yield, 56% after preparative TLC purification.

**10**: 56% yield; $^1$H NMR (500 MHz, 75% DMSO-$d_6$/25% $CDCl_3$) 8.20 (s, 1H, CONH, Ar), 7.41 (s, 1H, CONH), 7.39 (d, 2H, Ar), 7.20 (m, 5H, Ar), 6.93 (1H, CONH), 6.90 (2H, Ar), 3.95 (t, 2H, $CH_2$), 2.32 (s, 3H, $CH_3$), 2.30 (t, 2H, $CH_2$); HRMS *m*/*e* calcd for $C_{17}H_2ON_3O_2$ $[M + 1]^+$ 298.1540, found 298.1547.

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(7) Copper salts could not be completely washed from the resin after the reaction, but they could be easily resin-quenched from the cleaved material using Chelex resin and the product filtered off. Although polystyrene resin was used for all the syntheses described, we later found that the copper salts were more easily washed away from PEG resins. The N-arylation yields were similar for PEG and PS resins.

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