



## 2-Aryl propionamides via 1,4-aryl radical migration from *N*-arylsulfonyl-2-bromopropionamides

Andrew J. Clark\*, Stuart R. Coles, Alana Collis, David R. Fullaway, Nicholas P. Murphy, Paul Wilson

Department of Chemistry, University of Warwick, Coventry, West Midlands CV4 7AL, United Kingdom

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### ABSTRACT

Reaction of *N*-alkyl-*N*-arylsulfonyl-2-halo-propionamides with pentamethyldiethylenetriamine and either CuBr or CuCl leads to 2-aryl propionamides via initial radical generation, 1,4-aryl migration with loss of SO<sub>2</sub> and reduction of the intermediate amidyl radical in 40–99% yields.

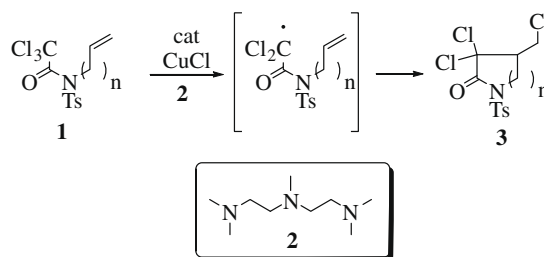
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Aryl transfer from sulfonamides with loss of SO<sub>2</sub> during radical reactions is well established and a range of migration types including 1,4- and 1,5-aryl migrations have been described.<sup>1</sup> The majority of these published procedures involve reactions mediated by toxic organostannane reagents under high dilution conditions. Copper(I) halide catalysed atom transfer radical cyclisation (ATRC) reactions of trichloroacetamides **1** have been extensively studied.<sup>2</sup> The majority of substrates reported contain an *N*-arylsulfonamide group and undergo rapid 5-*exo* or 6-*exo* radical cyclisations in excellent yields, Scheme 1.<sup>3</sup>

However, if cyclisations are relatively slow ( $n > 2$ ),<sup>3g</sup> or if there are no alkene or alkyne radical acceptors available (e.g., **4a**, X = Cl, R = *n*-dodecyl) then 2-aryl acetamide **6a** is produced (23%) via an alternative 1,4-aryl migration of initial radical **8a** at 50 °C.<sup>4</sup> Hence, *ipso* cyclisation of **8a** gives the cyclohexadienyl radical **9a** which after re-aromatisation and concomitant loss of SO<sub>2</sub> furnishes the amidyl radical **10a**. Reduction of **10a** by the solvent furnishes the observed amide **6a**. Competitive reduction of the initially produced radical **8a** to give **5a** (34%) also occurs and the ratio of **5a** to **6a** is temperature dependent with higher temperatures increasing the ratio towards the 1,4-aryl migration product **6a** (rt, **5a**:**6a** = 78:22; 50 °C, **5a**:**6a** = 60:40).<sup>4</sup> Unfortunately, hydrolysis to give **7** (R = *n*-dodecyl) in 12% yield also occurs and this competitive pathway, coupled with the formation of **5a**, does not make the formation of 2-aryl acetamides **6a** (X = Cl, R = alkyl) from trichloroacetamides **4a** (X = Cl,

R = alkyl) synthetically useful (8–47%).<sup>4</sup> We hypothesised that if we changed the nature of the initial radical from the electrophilic dichloroacetyl radical **8a** (X = Cl) to the more nucleophilic 2-methylpropionyl radical **8b** (X = Me) we would increase the rate of [1,5]-*ipso* substitution onto the relatively electron-poor phenylsulfonyl group (**8**→**9**) at the expense of reduction (**8**→**6**). In addition, the extra stability towards hydrolysis of simple propionamides **4b** (X = Me) compared to trichloroacetamides **4a** (X = Cl) would limit the amount of competing hydrolysis to **7** observed, Scheme 2.

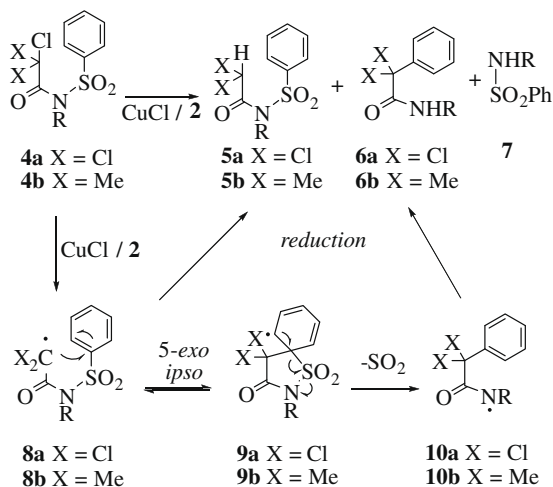
Our initial experiments tested this hypothesis by preparing a range of *N*-phenylsulfonamides varying in the electronic nature and hydrolysis susceptibility of the 'initiating' acyl group. We compared the trichloroacetamide **12a**, dichloroacetamide **12b**, bromoacetamide **12c** and bromodimethylacetamide **12d**, Scheme 3. The compounds were prepared from the corresponding sulfonamide



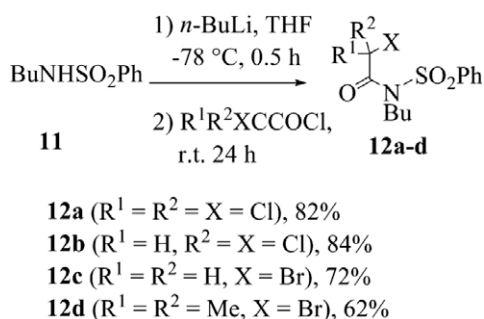
Scheme 1. ATRC of trichloroacetamide **1** with CuCl/**2**.

\* Corresponding author. Tel.: +44 2476 523242; fax: +44 2476 524112.

E-mail addresses: [a.j.clark@warwick.ac.uk](mailto:a.j.clark@warwick.ac.uk), [msrir@csv.warwick.ac.uk](mailto:msrir@csv.warwick.ac.uk) (A.J. Clark).



**Scheme 2.** Possible products from reaction of **4** with CuCl/2.



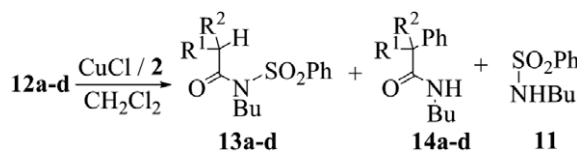
**Scheme 3.** Synthesis of amides **12a-d**.<sup>5</sup>

**11** by deprotonation with *n*-BuLi at  $-78^\circ\text{C}$  in dry THF followed by acylation with the appropriate acid chloride at rt.<sup>5</sup>

In copper(I)-mediated 5-*exo* ATRC reactions, 3° radicals generated from trihaloacetamides or bromodimethylacetamides are generally more reactive towards cyclisation than 2° radicals generated from dihaloacetamides which in turn are more reactive than 1° radicals derived from monohaloacetamides.<sup>2</sup> Thus, the rate and yield of cyclisations are generally increased by increasing the number of substituents at the initiating radical centre, presumably via the Thorpe–Ingold effect.<sup>6</sup> It follows that this trend might also be observed in the reactions of **12a-d**, as mechanistically their formation also requires a cyclisation (**8**→**9**). Taking this, and the electronic differences of the radicals into account, we would expect the ratio of 1,4-aryl migration **14** to reduction **13** to increase in the order of **12c** < **12b** < **12a** ≤ **12d**.

This trend was indeed observed with the relative proportions of 1,4-aryl transfer **14a-d** to reduction **13a-d** decreasing with decreasing radical substitution. For **12b-c**, a significant amount of ‘hydrolysis’ to **11** also occurred under the reaction conditions, Table 1. Gratifyingly, when the substrate **12d** was employed, no cleavage of the amide bond was detected and only a trace amount of the reduced product **13d** was isolated (<5%). Presumably, the more nucleophilic radical coupled with its tertiary nature facilitates 1,4-aryl transfer and the more stable amide bond ensures no cleavage of the amide under the reaction conditions. Carrying out the reaction of **12d** at room temperature decreased the selectivity for 1,4-aryl transfer **14d** as expected (run 4 vs 6, 50 °C, **13d:14d** = 5:95; rt, **13d:14d** = 53:47) and is in keeping with the temperature dependence for **12a** (run 1 vs 5, 50 °C,

**Table 1**  
Reactions of **12a-d** with CuCl or CuBr and ligand **2**



Run	Compd	Temp	Ratio 13:14:11 <sup>a</sup>
1	<b>12a</b>	Reflux	7:89:4
2	<b>12b</b>	Reflux	38:12:50 <sup>b</sup>
3	<b>12c</b>	Reflux	36:0:64
4	<b>12d</b> <sup>c</sup>	Reflux	5:95:0
5	<b>12a</b> <sup>c</sup>	rt <sup>d</sup>	54:34:12
6	<b>12d</b> <sup>c</sup>	rt <sup>d</sup>	40:35:25

<sup>a</sup> Ratio determined by <sup>1</sup>H NMR (300 MHz) spectroscopy of the crude mixture.

Reactions were carried out with substrate (0.3 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 ml) under nitrogen over 4 h.

<sup>b</sup> The reaction only proceeded to a 60% conversion after 4 h.

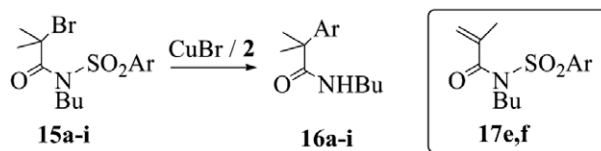
<sup>c</sup> Two equivalents of CuBr/2 were used.

<sup>d</sup> Reaction carried out over 24 h.

**13a:14a** = 7:93; rt, **13d:14d** = 61:39) and that reported for the related radical **8a** (X = Cl, R = *n*-dodecyl).<sup>4</sup> The reactions of **12a** and **12d** were sluggish and required 24 h at rt over which time significant decomposition to **11** occurred. Having shown a marginally better selectivity for 1,4-aryl migration for **12d** over **12a** could be achieved and that the reaction of **12d** could be accomplished with no competing amide cleavage to **11** at 50 °C, we next prepared a range of 2-bromodimethylacetamide derivatives **15a-i** in which we varied the aryl group of the sulfonamide both sterically and electronically, Table 2. These compounds were prepared using the same procedure described in Scheme 3, except significant amounts of methacrylates **17e-f** (20–30%) were isolated under these conditions, presumably from base-mediated elimination of HBr from the intermediate tertiary bromides **15e-f**, Table 2. This approach proved problematic for the preparation of **15i** and the base was modified as a consequence (Hünig’s base).

In all cases complete conversion into products **16a-i** occurred after refluxing in CH<sub>2</sub>Cl<sub>2</sub> for 4 h<sup>7</sup> with only minor traces (<5%) of the corresponding reduction **18a-i** and amide cleavage products **19a-i** detected in the crude <sup>1</sup>H NMR (300 MHz), Figure 1. On the other hand, if the reactions were carried out at rt instead of at reflux then significant amounts of competing reduction products **18**

**Table 2**  
Yields of sulfonamides **15a-i** and their reaction with CuBr/2



Run	Compd	Aromatic group	Yield <sup>a</sup> <b>15a-i</b> (%)	Yield <b>16a-i</b> (%)
1	<b>15a</b>	4-Me	56	55
2	<b>15b</b>	2,4,6-(Me) <sub>3</sub>	42	65
3	<b>15c</b>	4-OMe	48	40
4	<b>15d</b>	4-CF <sub>3</sub>	70	62
5	<b>15e</b>	4-NO <sub>2</sub>	32 <sup>b</sup>	99
6	<b>15f</b>	4-F	52 <sup>b</sup>	51
7	<b>15g</b>	4-CN	56	50
8	<b>15h</b>	2-Naphthyl	65	57
9	<b>15i</b>	3,5-(CF <sub>3</sub> ) <sub>2</sub>	67 <sup>c</sup>	61

<sup>a</sup> Compounds **15a-i** were prepared according to Scheme 3.

<sup>b</sup> Significant amounts of the methacrylates **17e,f** were isolated.

<sup>c</sup> This compound was prepared by reacting 3,5-di-trifluoromethylphenyl-sulfonyl chloride, Hunig’s base and 2-bromoisobutyl bromide at rt for 24 h.

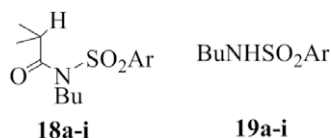
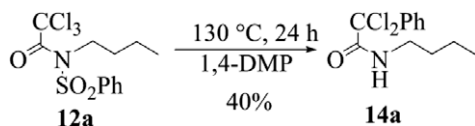


Figure 1. Structures of compounds **18a–i** and **19a–i**.

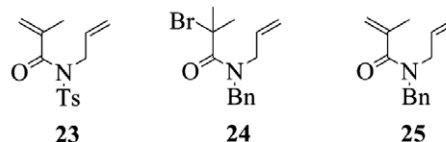
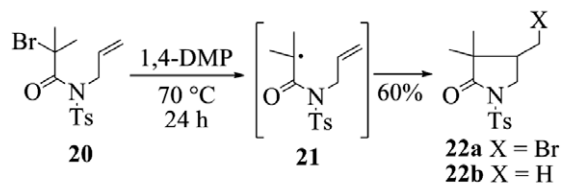
were isolated. This is in keeping with the observation that carrying out the reaction at lower temperature increases the amount of reduction observed.<sup>3</sup> Thus, treating **15d–f** with 2 equiv of CuBr/**2** in CH<sub>2</sub>Cl<sub>2</sub> at rt for 6 h furnished both **16e–f**:**18e–f** in the ratios (**15d** = 3:1, **15e** = 4:1 and **15f** = 6:1,<sup>8</sup> respectively). With the exception of the electron-rich aryl analogue **15c**, all the reactions proceeded to give 1,4-aryl transfer products **16** in average to high yields (50–99%).

Recently, Ishibashi reported radical cyclisations of trichloroacetamides under reductive conditions using 1,4-dimethylpiperazine (1,4-DMP) as a reactant/solvent.<sup>9</sup> No other additives were required. Organic amines can act as electron donors in single electron transfer reactions and 1,4-DMP was shown to generate radicals from trichloroacetamides by cleavage of a carbon–chlorine. We showed that heating trichloroacetamide **12a** in 1,4-DMP to 130 °C facilitated a 1,4-aryl transfer to give **14a** in low yield (40%), Scheme 4.<sup>4</sup> Interestingly, only traces of the corresponding reduced **13a** and hydrolysed **11** products were isolated (compared to **13a**:**14a**:**11** = 54:34:12 ratio at rt in CH<sub>2</sub>Cl<sub>2</sub>), presumably due to the increased temperature at which the reactions were carried out. To our knowledge, only trichloroacetamide substrates have been used in successful 1,4-DMP-mediated radical reactions. We were intrigued therefore to see if the same approach could be used to generate radicals from bromodimethylacetamides (e.g., **12d**) where radical initiation through cleavage of the carbon–halogen bond would be more difficult.

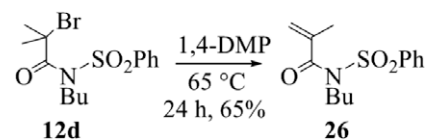
Initially, we were encouraged when we discovered that heating **20** in dry 1,4-DMP at 70 °C in a sealed tube led to the two cyclised products **22a** and **22b** in a 60% combined yield (ratio of **22a**:**22b** = 1:8). Presumably **22a** is produced via a conventional atom transfer cyclisation with intermediate radical **21** abstracting a bromine atom from a molecule of starting material **20**, while the major product **22b** arises from abstraction of a hydrogen atom from the solvent. The reaction was quite capricious and we found that scrupulous drying (over 4 Å MS followed by reduced pressure distillation) of 1,4-DMP was required for success. Trace amounts of water led not to cyclisation, but elimination to give **23**. This result is important as it shows that it is possible to generate radicals from tertiary bromides using 1,4-DMP under conditions that do not lead to elimination of the tertiary bromide. Unfortunately, for slower cyclisations, such as that of **24** these conditions were not successful. Instead, the reaction was sluggish and 73% of starting material **24** was recovered along with 6% of eliminated product **25** after three days. Facilitating the reaction in a mixed solvent of DMSO:1,4-DMP (1:1) at 65 °C improved the conversion but the eliminated product **25** was the sole product isolated in 75% yield after three days, Scheme 5. Hence, it came as no surprise that the elimination pathway to give **26** was also observed when 1,4-aryl transfer precursor **12d** was heated with 1,4-DMP under the same reaction conditions, Scheme 6.



Scheme 4. Reaction of **12a** with 1,4-DMP.



Scheme 5. Radical cyclisation of **20** with 1,4-DMP.



Scheme 6. Attempted 1,4-aryl rearrangement of **12d** mediated by 1,4-DMP.

In conclusion, we have shown that the reaction of sulfonamides **12a–d**, and **15a–i**, with either CuCl or CuBr and amine ligand **2** furnishes rearranged amides **14a–d**, and **16a–i** via radical generation (**8**), 1,4-aryl migration (with loss of SO<sub>2</sub>) and reduction of the intermediate amidyl radical **10**. For dichloroacetyl **12b** and monobromoacetyl **12c** derivatives the reaction yield is often compromised by competitive reduction of the initial carbon radical **8** by the solvent to give **13b–c** and by decomposition to give **11** with the relative amount of 1,4-aryl transfer increasing with increasing substitution of the initiating radical **12c** > **12b**. Changing the nature of the initiating radical from a 1° or 2° radical to a 3° radical (e.g., **12a,d**) facilitates 1,4-aryl transfer over the other competing reaction pathways, presumably through the Thorpe–Ingold effect. The selectivity for 1,4-aryl migration is marginally better for the more nucleophilic radical **12d** compared to **12a**. Thus, *N*-alkyl-*N*-(2-bromo-2-methylpropionyl)-sulfonamides **15a–i** furnish 2-aryl propionamides in synthetically acceptable yields (40–99%). While attempts to facilitate the rearrangement of **12d** reductively using 1,4-DMP failed, it was possible to mediate a 5-*exo* radical cyclisation of bromo substrate **20**, indicating that 1,4-DMP can generate radicals not only from reactive trichloroacetamide derivatives, but also from other tertiary halides.

## Acknowledgement

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5. A typical procedure is illustrated for **12d**. A 2.5 M solution of *n*-butyllithium (4.4 ml, 12.0 mmol) was added dropwise over 5 min to a stirred solution of *N*-butylbenzenesulfonamide **11** (2.13 g, 10 mmol) in anhydrous THF (100 ml) under nitrogen at  $-78^{\circ}\text{C}$ . After 30 min, 2-bromoisobutryl bromide (2.68 g, 12.0 mmol) was added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  solution (10 ml), and was partitioned between  $\text{CH}_2\text{Cl}_2$  (200 ml) and saturated  $\text{NaHCO}_3$  (200 ml). The layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 100$  ml). The combined organic extract was washed with brine (200 ml), dried ( $\text{MgSO}_4$ ) and the solvent was removed in vacuo to give **12d** as a white crystalline solid, (1.60 g, 62%) after chromatography (9:1 petroleum ether:ethyl acetate). Data for **10d**: mp  $98\text{--}100^{\circ}\text{C}$ ;  $\text{C}_{14}\text{H}_{20}\text{BrNO}_3\text{S}$  requires C, 46.4; H, 5.6; N, 3.9; found: C, 46.4; H, 5.5; N, 3.8. IR  $\nu_{\text{max}}$  2955, 1675, 1346, 1166, 1069, 723  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.98 (2H, d,  $J = 7.5$  Hz), 7.65 (1H, t,  $J = 7.5$  Hz), 7.54 (2H, t,  $J = 7.5$  Hz), 4.19 (2H, app t,  $J = 8.0$  Hz), 1.92 (2H, m), 1.89 (6H, s), 1.41 (2H, quin,  $J = 7.0$  Hz), 0.99 (3H, t,  $J = 7.0$  Hz);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ) 170.5, 139.3, 133.5, 128.7 ( $\times 2$ ), 128.5 ( $\times 2$ ), 56.6, 48.5, 33.0, 31.8 ( $\times 2$ ), 20.0, 14.0; EI-MS  $m/z$  362 (MH)<sup>+</sup>. EI-MS found 362.0425,  $\text{C}_{14}\text{H}_{21}\text{NO}_3\text{SBr}^{79}$  requires 362.0425.
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7. A typical procedure is illustrated for **12d**. Substrate **12d** (0.3 mmol) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (2 ml) and CuBr (0.6 mmol) and pentamethyldiethylenetriamine **2** (0.6 mmol) were added. The reaction mixture was heated at  $50^{\circ}\text{C}$  for 4 h. After cooling, the crude mixture was passed through a small silica plug (eluted with ethyl acetate, 20 ml to remove the copper residues). After evaporation of the solvent and column chromatography (8:1 petroleum ether:ethyl acetate), *N*-butyl-2,2-dimethyl-2-phenylacetamide **14d** was isolated in 70% yield. Data for **14d**.  $\text{C}_{14}\text{H}_{21}\text{NO}$  requires C, 76.6; H, 9.7; N, 6.3; found: C, 76.0; H, 9.7; N, 6.3. IR  $\nu_{\text{max}}$  3358, 2928, 1643, 1525, 1365, 1164, 762  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.32 (2H, d,  $J = 6.9$  Hz), 7.21 (3H, m), 5.18 (1H, br s), 3.09 (2H, q,  $J = 7.0$  Hz), 1.49 (6H, s), 1.31 (2H, quin,  $J = 7.0$  Hz), 1.19 (2H, app sex, 7.0 Hz), 0.78 (3H, t,  $J = 7.0$  Hz);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ) 177.4, 145.3, 128.7 ( $\times 2$ ), 127.0, 126.5 ( $\times 2$ ), 39.4, 31.5, 29.7 ( $\times 2$ ), 27.1, 20.0, 14.0. EI-MS found 219.1624,  $\text{C}_{14}\text{H}_{21}\text{NO}$  requires 219.1623.
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