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1,4-Aryl migration under copper(I) atom transfer conditions

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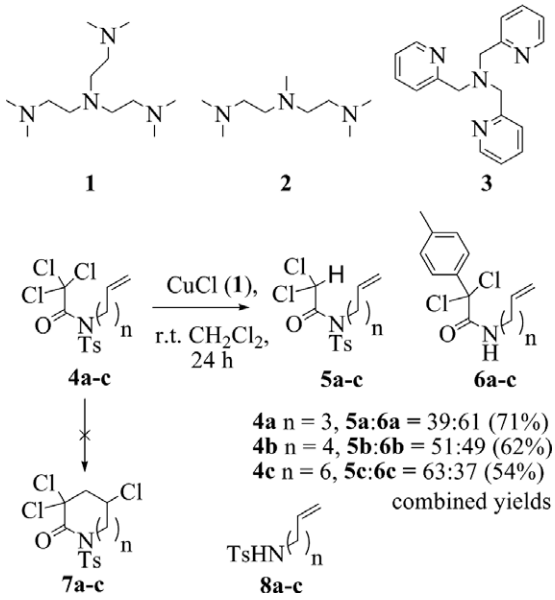
ABSTRACT

Reaction of *N*-alkyl-*N*-(trichloroacetyl)arylsulfonamides with CuCl/amines leads to *N*-alkyl-*N*-(dichloroacetyl)-arylsulfonamides via reduction or *N*-alkyl-aryldichloroacetamides via 1,4-aryl migration with loss of SO_2. The ratio of reduction to aryl migration is dependent upon the temperature and the ligand utilised. Along with amide bond hydrolysis these reactions may compete when carrying out slow atom transfer radical cyclisation reactions using sulfonamides.

Copper(I) halide-catalysed atom transfer radical cyclisation (ATRC) reactions have been extensively studied.[1] The majority of the published procedures utilise CuCl in combination with amine ligands such as bipyridine (bpy),[2] *N*-(*n*-butyl)pyridylmethanimine (BPMI),[3] tetramethyl-ethylenediamine (TMEDA),[4] tris[2-(dimethylamino)-ethyl]amine (Me_6-tren)[5] **1**, pentamethyldiethylenetriamine (PMDETA)[6] **2** or tris[(2-pyridyl)methyl]amine (TPMA)[7] **3**. While most studies have involved cyclisations which proceed to give four- to six-membered rings there has been less research on the formation of medium-to-large-sized rings.[1] Speckamp and others[6,8] have reported that 8- to 12-membered rings can be successfully prepared in high yield using CuCl and bpy or TPMA **3** as ligands. These reactions have been restricted to cyclisation to give lactones. In order to extend the methodology to the synthesis of medium ring lactams we investigated the cyclisation of amides **4a–c** ($n = 3$, 4 and 6) under typical atom transfer conditions (Scheme 1). We did not detect any products **7a–c** arising from cyclisation, instead only products **5a–c** derived from reduction and amides **6a–c** from apparent 1,4-aryl migration with loss of SO_2 were isolated. Trace amounts of hydrolysed amides **8a–c** (5%) were also isolated. Thus, it seems that while relatively rapid atom transfer cyclisations of *N*-tosyl trichloracetamides (4-*exo*, 5-*exo*)[2,7b] occur in high yields, other competing pathways can occur for slow cyclisations.

Aryl transfer from sulfonamides with loss of SO_2 during radical reactions is well established and a range of migration types including 1,4- and 1,5-aryl migrations have been described.[9] However, the majority of published procedures involve reactions mediated by toxic organostannane reagents under high dilution conditions.

Mechanistically, the rearranged products **6a–c** may arise by *ipso* cyclisation of the radical **9** to give the spirocyclohexadienyl radical **10** which can rearomatise with cleavage of the aryl-S bond and loss of SO_2 to furnish the reactive amidyl radical **11** (Scheme 2).[9]



Scheme 1. Reaction to give reduced **5a–c** and aryl-migrated **6a–c** products.

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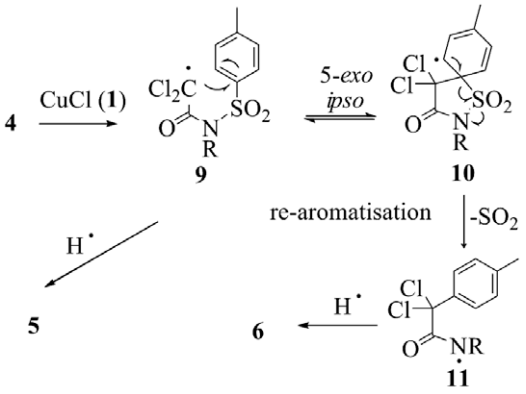


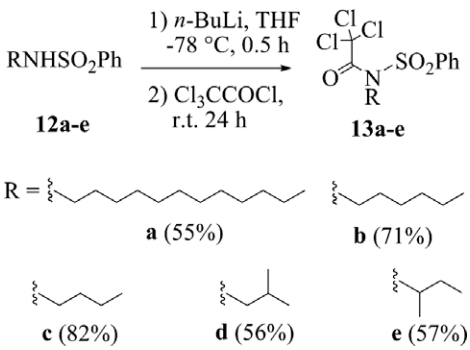
Scheme 2. Possible mechanisms for the formation of **5** and **6**.

Reduction of this amidyl radical via H abstraction from the solvent or the ligand furnishes the observed amides **6a–c**. Competitive reduction of the radical **9** leads to the products **5a–c**. Thus, the nature of the solvent and the ligand employed may be expected to affect the ratio of these products by altering the efficiency of the reduction (**9**→**5** and **11**→**6**). The reactions were notable in that they did not require high dilution conditions. In order to investigate this copper-mediated 1,4-aryl migration reaction further, we prepared compounds **13a–e** (Scheme 3). We chose to look at saturated chains attached to nitrogen in order to remove the potential complication of radical cyclisation. The compounds were prepared from the corresponding sulfonamides **12a–e**[10] by deprotonation with *n*-BuLi at −78 °C in dry THF followed by acylation with trichloroacetyl chloride.

Initial experiments involved heating amides **13a–e** at elevated temperatures (110 °C in toluene) with 1 equiv of CuCl and ligands **1–3**. Unfortunately, this caused decomposition of the starting material to give the sulfonamides **12a–e**. We thus shortened the reaction time to 4 h, in CH_2Cl_2 at reflux and screened the reaction of compound **13a** varying the catalyst **1–3** and solvent, Table 1.[11]

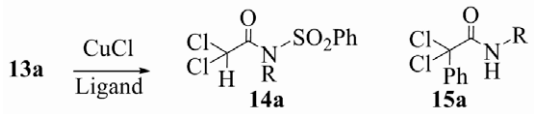
Comparing ligands **1–3** in the reaction of **13a** (runs 1–3) it is apparent that a significant amount of cleavage of the trichloroacetamide group to give **12a** occurs with ligands **1** and **3**. This may arise from hydrolysis of either the trichloroacetyl group in **13a** or the dichloroacetyl group in **14a** under the reaction conditions. The relative amount of 1,4-aryl migration was found to increase in the order of ligands **3** < **1** < **2**. In fact, no 1,4-aryl migration was observed when **3** was used as ligand (run 3). Decreasing the temperature (run 4) decreased the relative amount of migration. Having ascertained that 1,4-aryl migration was facilitated best using ligand **2** we briefly investigated the effect of solvent on the reaction of **13a** using this ligand. Surprisingly, we found relatively little difference in the ratio of products **14a**:**15a** produced with either CH_2Cl_2, MeCN or THF (runs 2, 5 and 6). Consequently, we chose to investigate the reactions of **13a–e** using ligand **2** in CH_2Cl_2 at rt and at reflux, Table 2. Temperature proved to be an important variable in controlling the relative amount of 1,4-aryl migration for the majority of substrates **13b–e**. For these substrates, selectivity was reversed on increasing the temperature from rt to reflux (compare runs 3/4, 7/8, 10/11 and 12/13, Table 2). The reaction of **13a** did not show such a substantial reversal of selectivity upon heating, however, the relative proportion of 1,4-aryl transfer did increase (runs 1 and 2), and as before, we investigated briefly the effect of changing the nature of the ligand **1–3** on the reaction of **13c**. As before, the relative amount of 1,4-aryl migration was found to increase in the order of ligands **3** < **1** < **2** with no migration detected for ligand **3**.

Having shown that different *N*-alkyl groups were tolerated we briefly investigated the effect of the *N*-sulfonyl group on the efficiency of migration in compounds **16a–c**, Figure 1, Table 3. Reaction of both the 2-naphthyl **16a** and the hindered mesityl derivative **16c** proceeded as expected in that the ratio of 1,4-aryl transfer to reduction increased with higher temperatures, (although for **16a** the aryl transfer pathway was still not the major outcome even at reflux). On the other hand, the electron-poor sub-



Scheme 3. Synthesis of amides **13a–e**.

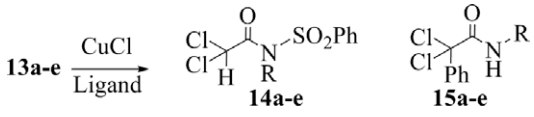
Table 1
Reactions of **13a** with CuCl and ligands **1–3**



Run	Solvent	Ligand	Temperature	Ratio[a] **12a**:**14a**:**15a**
1	CH_2Cl_2	**1**	Reflux	40:50:10
2	CH_2Cl_2	**2**	Reflux	12:53:35[b]
3	CH_2Cl_2	**3**	Reflux	43:57:0
4	CH_2Cl_2	**2**	rt	0:78:22[b]
5	MeCN	**2**	50 °C	16:63:21
6	THF	**2**	50 °C	13:50:37

[a] Ratio determined by ^{1}H NMR (300 MHz) of the crude mixture. Reactions were carried out with 0.3 mmol of substrate in dry solvent (2 mL) under nitrogen.
[b] Two equivalents of CuCl/**2** were used.

Table 2
Reactions of **13a–e** with CuCl and ligands **1–3**



Run	Substrate	Ligand	Temperature	Mass[a] balance	Ratio[b] **14**:**15**
1	**13a**	**2**	rt	38% (0%)	78:22[c]
2	**13a**	**2**	Reflux	57% (12%)	60:40[c]
3	**13b**	**2**	rt	39% (10%)	88:12[c]
4	**13b**	**2**	Reflux	47% (5%)	0:100[c]
5	**13c**	**1**	rt	80% (20%)[d]	80:20
6	**13c**	**1**	Reflux	83% (12%)[d]	60:40
7	**13c**	**2**	rt	38% (5%)	62:38[c]
8	**13c**	**2**	Reflux	49% (2%)	7:93[c]
9	**13c**	**3**	rt	85% (15%)[d]	100:0
10	**13d**	**2**	rt	35% (0%)	96:4[c]
11	**13d**	**2**	Reflux	36% (0%)	0:100[c]
12	**13e**	**2**	rt	36% (0%)	57:43[c]
13	**13e**	**2**	Reflux	31% (0%)	6:94[c]

[a] Mass of **14**:**15**. Figure in parentheses equates to percentage of **13a–e** isolated.
[b] Ratio determined by ^{1}H NMR (300 MHz) of the crude mixture. Reactions were carried out with 0.3 mmol of substrate in anhydrous CH_2Cl_2 (2 mL) under nitrogen.
[c] Two equivalents of CuCl/**2** were used.
[d] Reactions carried out over 24 h.

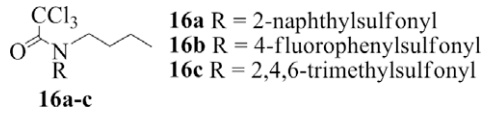
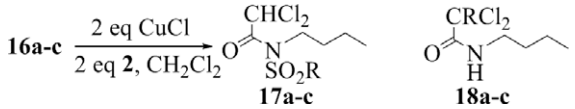


Figure 1. Substrates **16a–c**.

Table 3
Reaction of **16a–c** with CuCl/**2** in CH_2Cl_2



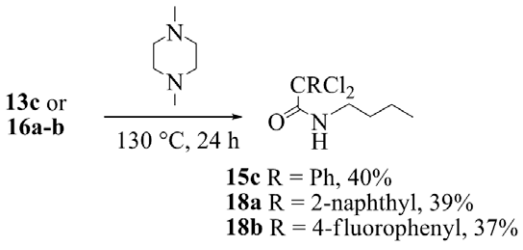
Compound	Temperature	Mass[a] balance	Ratio[b] **7**:**18**
16a	rt	55% (11%)	88:12
16a	Reflux	51% (8%)	66:34
16b	rt	26%	[c]
16b	Reflux	48%	[c]
16c	rt	39% (0%)	72:28
16c	Reflux	59% (0%)	38:62

[a] Mass of **17**:**18**, figure in parentheses equates to percentage of hydrolysed amide isolated.
[b] Ratio determined by ^{1}H NMR (300 MHz) of the crude mixture.
[c] The crude NMR indicated the presence of many products, the ratios were not determined but the major product was **17b**.

strate **16b** was more problematic in that the reactions were not clean and the only unambiguously assigned product isolated was that arising from reduction to give **17b** irrespective of the temperature.

Recently, Ishibashi reported radical cyclisations of trichloroacetamides under reductive conditions using 1,4-dimethylpiperazine (1,4-DMP) as the reactant/solvent.[12] 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 bond. As our reactions are reductive in nature we briefly explored whether it was possible to mediate the 1,4-aryl transfer using this protocol without the need for copper chloride. Heating **13c**, **16a** or **16b** (0.3 mmol) with 1,4-DMP (2 ml) at 130 °C overnight in a sealed tube followed by removal of the 1,4-DMP in vacuo and chromatography produced the expected 1,4-aryl transfer products **15c**, **18a** and **18b** in 40%, 39% and 37% yields, respectively (Scheme 4). Interestingly, only traces of the corresponding reduced and hydrolysed products were isolated, presumably due to the increased temperature at which the reactions were carried out. Thus, while the fluoro-derivative **16b** underwent mainly reduction to **17b** using CuCl/**2** either at rt or at 50 °C, only the 1,4-aryl transfer product **18b** was isolated when 1,4-DMP was used at 130 °C.

In conclusion, we have shown that reaction of trichloroacetylsulfonamides **4a–c**, **13a–e** and **16a–c**, with CuCl and amine ligands (**1–3**) furnishes rearranged amides **6a–c**, **15a–e** and **18a–c** via radical generation **9**, 1,4-aryl migration (with loss of SO_2) and



Scheme 4. Reaction of **13c** and **16a–b** with 1,4-DMP at 130 °C.

reduction of the intermediate amidyl radical **11**. The reaction yield is often compromised by the competitive reduction of the initial carbon radical **9** by the solvent and decomposition (hydrolysis) of the starting materials under the reaction conditions. Increasing the temperature generally increases the relative amount of 1,4-aryl migration at the expense of reduction, and in some cases, leads to total selectivity for rearrangement (runs 4 and 11, Table 2). Heating trichloroacetamides **13c** and **16a**, **b** in 1,4-DMP at 130 °C without CuCl also facilitated 1,4-aryl transfer in the trichloroacetamide derivatives. The results described here suggest that if carrying out relatively slow atom transfer or other slow radical cyclisation reactions on compounds containing suitably pendant sulfonyl groups, care should be taken to minimise competing aryl migration by using a low reaction temperature.

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10. *A typical procedure is illustrated for compound* **13c**. 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 **12c** (2.13 g, 10 mmol) in anhydrous THF (100 ml) under nitrogen at −78 °C. After 30 min trichloroacetyl chloride (1.34 ml, 12.0 mmol) was added and the reaction mixture was allowed to warm to rt overnight. The reaction was quenched with saturated NH_4Cl solution (10 ml), and the reaction mixture was partitioned between CH_2Cl_2 (200 ml) and

saturated $NaHCO_3$ (200 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 ml). The combined organic extracts were washed with brine (200 ml), dried ($MgSO_4$) and the solvent was removed in vacuo to give *N*-butyl-*N*-(2,2,2-trichloroacetyl)-benzenesulfonamide **13c** as a white crystalline solid, (2.9 g, 82%) after chromatography (5:1 petroleum ether:ethyl acetate). Mp 81–83 °C. $C_{12}H_{14}Cl_3NO_3S$ requires: C, 40.2; H, 3.9; N, 3.9. Found: C, 40.2; H, 3.9; N, 3.9. ν_{max} 2972, 1705, 1359, 1169 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.04 (2H, d, *J* = 7.5 Hz), 7.68 (1H, t, *J* = 7.5 Hz), 7.57 (2H, d, *J* = 7.5 Hz), 4.18 (2H, t, *J* = 7.5 Hz), 1.98 (2H, m), 1.40 (2H, m), 1.00 (3H, t, *J* = 7.5 Hz). EI-MS *m/z* 357.9 (MH^+), 301.8 ($MH^+-C_4H_8$).

11. *A typical procedure is illustrated for reaction of* **13c** (Table 2, entry 8). Substrate **13c** (0.3 mmol) was dissolved in dry CH_2Cl_2 (2 ml) and CuCl (0.6 mmol) and pentamethyldiethylenetriamine **2** (0.6 mmol) was added. The reaction mixture was heated at 50 °C for 4 h. Upon cooling the crude mixture was passed through a small silica plug (eluting with ethyl acetate, 20 ml to remove the copper residues). After evaporation of the solvent *N*-butyl-2,2-dichloro-*N*-(phenylsulfonyl)acetamide **14c** and *N*-butyl-2,2-dichloro-2-phenylacetamide **15c** were isolated in the ratio 7:93. Chromatography (3:1 petroleum ether:ethyl acetate). Data for **14c**, white crystalline solid, mp 35–36 °C. Found 346.0047, $C_{12}H_{15}Cl_2NO_3S$ $(M+Na)^+$ requires 346.0048. ν_{max} 2972, 1705, 1448, 1171 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.93 (2H, d, *J* = 7.5 Hz), 7.72 (1H, t, *J* = 7.5 Hz), 7.59 (2H, d, *J* = 7.5 Hz), 6.91, (1H, s), 3.70 (2H, t, *J* = 7.8 Hz), 1.60 (2H, m), 1.38–1.11 (2H, m), 0.85 (3H, t, *J* = 7.8 Hz). EI-MS *m/z* 324 (MH^+), 268 ($MH^+-C_4H_8$). Data for **15c**, clear oil. Found 282.0423, $C_{12}H_{15}Cl_2NO$ $(M+Na)^+$ requires 282.0423. ν_{max} 3333, 2957, 1673, 1311, 1156 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.63 (2H, m), 7.34 (3H, m), 6.82 (1H, br s), 3.27 (2H, q, *J* = 7.0 Hz), 1.49 (2H, quin, *J* = 7.0 Hz), 1.29 (2H, sex, *J* = 7.0 Hz), 0.85 (3H, t, *J* = 7.0 Hz). ESI-MS *m/z* 282 $(M+Na)^+$, 160.

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