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Microwave-assisted N-arylation of a sulfoximine with aryl chlorides

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Abstract—*N*-Arylsulfoximines and related species could be prepared in good to excellent yield by the palladium-catalyzed coupling of **1** with aryl chlorides under the influence of microwave irradiation.

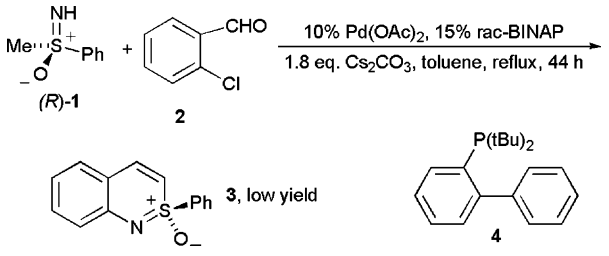
As part of our continuing research of the synthesis and chemistry of enantiomerically pure benzothiazines, we maintain an active interest in the N-arylation of sulfoximines. This process, first reported by Bolm and Hildebrand,[1] was key to our discovery of a facile synthesis of enantiomerically pure benzothiazines.[2] The Bolm group has made use of this reaction in the preparation of a variety of chiral ligands and unique cyclic sulfoximines.[3] We have also developed a chiral ligand based on this chemistry and have recently introduced the stereoselective, intramolecular addition of sulfoximine carbanions to α,β-unsaturated esters as a means of preparing chiral, enantiomerically pure benzothiazines.[4,5] This methodology has been extended to the formal total syntheses of (+)-curcuphenol and (+)-curcumene.[6]

Typically, the Bolm methodology has been used to couple aryl bromides to N–H sulfoximines. Aryl iodides and triflates have also been shown to be suitable coupling partners.[7] To the best of our knowledge, the coupling of aryl chlorides to N–H sulfoximines is unknown.[8]

We were curious as to whether the Bolm reaction conditions could be applied to aryl chlorides. Our first attempts to couple aryl chlorides with sulfoximine resulted in poor yields of products. For example, the reaction of 2-chlorobenzaldehyde with 4 equiv of **1** in the presence of 3 equiv of cesium carbonate and catalytic amounts of $Pd(OAc)_2$ in refluxing toluene for 44 h afforded a complex mixture in which only a small amount of benzothiazine **3** was detected. Switching to ligand **4**[9] and using either sodium *tert*-butoxide or K_3PO_4 as base gave less than 10% yields of **3**, in addition to small amounts of a condensation product (Scheme 1).

Rather than perform a catalyst optimization study, we wondered whether the intense and rapid heating associated with microwave irradiation might make it possible to use aryl chlorides as partners in the arylation reaction of **1**.[10] This report is a summary of our studies.

Our results are summarized in Table 1. We used four different procedures in an effort to get a preliminary indication as to how certain changes in reaction conditions would affect the outcome of the N-arylation process.[11] Procedure A involved irradiating a solution of 1.2 equiv **1** and an aryl chloride in the presence of 5% $Pd(OAc)_2$, 7.5% *rac*-BINAP, and 1.4 equiv of Cs_2CO_3. These are essentially Bolm's conditions for the thermal coupling of aryl bromides. In procedure B, 5 equiv of aryl chloride were used and the reaction was run through two 1.5 h cycles, new catalyst and ligand being added prior to the start of the second cycle. With procedure C aryl chlorides were used as the solvent and two



Scheme 1.

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Table 1. Microwave-assisted reaction of **1** with aryl chloride under palladium catalysis

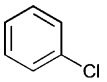
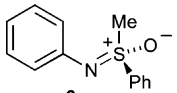
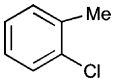
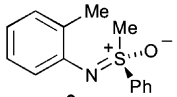
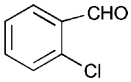
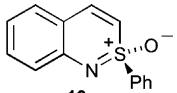
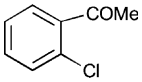
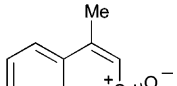
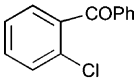
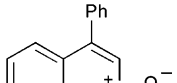
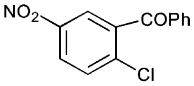
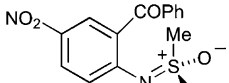
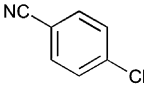
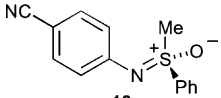
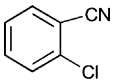
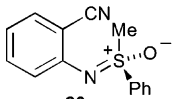
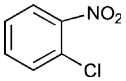
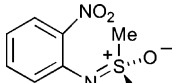
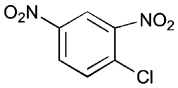
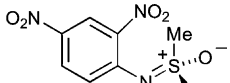
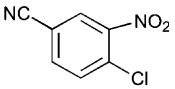
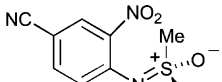
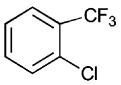
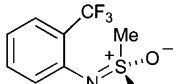
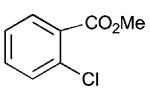
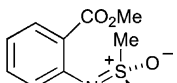
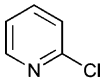
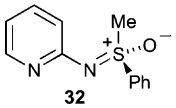
Entry	Aryl chloride	Method	Product	Yield (%)
1	 **5**	A	 **6**	10
2	**5**	A[a]	**6**	33
3	**5**	C	**6**	49
4	 **7**	C	 **8**	47
5	 **9**	A	 **10**	55
6	**9**	B	**10**	87
7	 **11**	B	 **12**	31
8	 **13**	B	 **14**	74
9	 **15**	B	 **16**	90
10	 **17**	B	 **18**	94
11	 **19**	B	 **20**	93
12	 **21**	B	 **22**	74
13	 **23**	B	 **24**	80
14	 **25**	B	 **26**	94
15	 **27**	B	 **28**	72
16	 **29**	B	 **30**	46

Table 1 (*continued*)

Entry	Aryl chloride	Method	Product	Yield (%)
17	**29**	D	**30**	65
18	 **31**	B	 **32**	43

[a] Ten equivalents of aryl chloride were used.

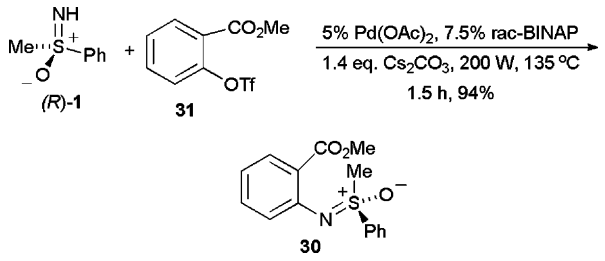
cycles of irradiation were used, as in procedure B. Procedure D was similar to procedure B, but with 15% *t*-Bu_3P replacing BINAP.

As successful as Bolm reagent blend is for aryl bromides under thermal conditions, it appeared in certain experiments that aryl chloride reduction was taking place or that catalyst was simply losing activity over time. For example, when chlorobenzene was treated with **1** in the presence of palladium acetate and *rac*-BINAP and the mixture irradiated for 1.5 h at 135 °C (200 W), the sulfoximine **6** was produced in only 10% yield (entry 1). Using 10 equiv of chlorobenzene increased the yield to 33% (entry 2) and using the reactant as solvent afforded a 49% yield of **6** (entry 3). A similar result was obtained when 2-chlorotoluene was used as solvent (entry 4). These are not bad results, given that no attempt was made to improve the catalyst system.

However, we were more interested in aryl chlorides bearing electron-withdrawing groups, not only because some of them could be converted to benzothiazines, but also because we anticipated that they would function better in the coupling reaction. This turned out to be the case. For example, when 2-chlorobenzaldehyde **9** was coupled to **1**, benzothiazine **10** was produced in 55–87% yield, depending on the procedure used (entries 5 and 6). Even 2-chloroacetophenone coupled with **1** to give **12**, albeit in only 31% yield (entry 7). Interestingly, while **13** produced the expected benzothiazine **14** in 74% yield (entry 8), its nitrated analogue **15** gave only the corresponding *N*-arylsulfoximine **19** in 90% yield (entry 9). It is possible that the nitro group increases the stability of the sulfoximine carbanion derived from **19** sufficiently well that it is simply not reactive enough to engage in addition to the carbonyl group.

Various other chloroarenes were used as coupling partners with **1** and in general, the corresponding sulfoximines were produced in excellent yield (entries 10–15). One notable exception was the sulfoximine **30** derived from ester **29**, which was formed in only 46% yield. This yield could be improved by irradiating **1** with 5 equiv of the aryl chloride in the presence of $Pd(OAc)_2$ and *t*-Bu_3P for the usual time (entry 17).

We were curious to see if the yield of **30** might be improved by using a different starting material. Thus, we prepared triflate **31** and treated it with 1.2 equiv of **1** under reaction conditions corresponding to Procedure A. We isolated **30** in 94% yield (Scheme 2). When 5 equiv of sulfoximine were used, the yield improved to 99%.



Scheme 2.

In summary, we have developed a simple procedure for the rapid N-arylation of sulfoximine **1** with aryl chlorides. Appropriately functionalized systems gave rise to benzothiazines directly in a one pot process. One aryl triflate was shown to react very well to form an *N*-aryl sulfoximine. Optimization of catalyst systems or development of conditions that avoid any catalysts[12] are under study. Further results will be reported in due course.[13,14]

Acknowledgements

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11. General procedures for coupling: A: A 10 mL microwave tube equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%), and toluene (5 mL) under an N_2 atmosphere. Aryl chloride (1.0 equiv) was added, followed by **1** (1.2 equiv), and cesium carbonate (1.4 equiv). The reaction mixture was stirred at room temperature for 30 min, then heated in the microwave reactor with vigorous stirring for 1.5 h at 135 °C (constant temperature) at 200 W. The reaction was cooled down and diluted with dichloromethane, filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by flash chromatography (30–40% EtOAc/hexanes). B: As in procedure A. However after the initial irradiation, the reaction was cooled and $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%) were added. The reaction mixture was heated in the microwave reactor with vigorous stirring for another 1.5 h at 135 °C (constant temperature) at 200 W. The reaction was cooled down and diluted with dichloromethane, filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by flash chromatography (30–40% EtOAc/hexanes). C: Same procedure as B, but 5 mL of aryl chloride was used as solvent instead of toluene. D: A 10 mL microwave tube equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5 mol%) and tri-*tert*-butyl-phosphane (15 mol%) under an N_2 atmosphere. Aryl chloride (1.5 mmol, 5.0 equiv) was added, followed by **1** (0.3 mmol, 1.0 equiv), and cesium carbonate (0.42 mmol, 1.4 equiv). The reaction mixture was stirred at room temperature for 30 min, then heated in the microwave reactor with vigorous stirring for 1.5 h at 135 °C (constant temperature) at 200 W. The reaction was cooled down and diluted with dichloromethane, filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by flash chromatography (30–40% EtOAc/hexanes).
12. Xu, G.; Wang, Y.-G. *Org. Lett.* **2004**, *6*, 985.
13. All new compounds were characterized by proton and carbon NMR and high resolution mass spectrometry.
14. Data for new compounds: **8**: Procedure C, colorless liquid, yield 47%; IR: 3064, 3015, 2925, 1597, 1491, 1446, 1294 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98–7.96 (m, 2H), 7.57–7.56 (m, 1H), 7.53–7.49 (m, 2H), 7.11 (dd, $J = 7.6$, 0.5 Hz, 1H), 7.00 (dd, $J = 7.8$, 0.9 Hz, 1H), 6.90 (td, $J = 7.4$, 1.1 Hz, 1H), 6.80 (td, $J = 7.4$, 1.1 Hz, 1H), 3.20 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 139.8, 133.0, 132.1, 130.3, 129.4, 128.3, 126.2, 121.7, 121.6, 45.5, 18.6; HRMS calcd for $C_{14}H_{15}NOSNa$ $[M+Na]^+$ 268.0766; Found: 268.0773; $[\alpha]_D^{25}$ −70.04 (*c* 4.56, $CHCl_3$). **12**: Procedure B, pale yellow solid, yield 31%, mp: 113–115 °C; IR: 3060, 2949, 2904, 1601, 1580, 1527, 1450, 1331, 1249, 1209 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.90–7.86 (m, 2H), 7.63–7.32 (m, 6H), 7.07–7.00 (m, 1H), 6.26 (s, 1H), 2.47 (d, $J = 0.7$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 146.8, 145.2, 141.7, 133.0, 131.7, 128.9, 128.6, 125.0, 124.7, 119.9, 117.3, 108.4, 20.9; HRMS calcd for $C_{15}H_{13}NOSNa$ $[M+Na^+]$ 278.0610; Found: 278.0608. **14**: Procedure B, pale semi-solid, yield 74%; IR: 3064, 1609, 1560, 1531, 1339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97–7.90 (m, 2H), 7.57–7.34 (m, 10H), 6.97–6.91 (m, 1H), 6.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 145.8, 141.3, 137.1, 133.2, 131.8, 129.0, 128.9, 128.8, 128.4, 128.0, 124.6, 119.9, 116.9, 108.4; HRMS calcd for $C_{20}H_{15}NOSNa$ $[M+Na]^+$ 340.0766; Found: 340.0781; $[\alpha]_D^{25}$ −174.5 (*c* 3.62, $CHCl_3$). **16**: Procedure B, yellow oil, yield 90%; IR: 3060, 3035, 2933, 2255, 1666, 1593, 1470, 1290 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.17 (d, $J = 2.7$ Hz, 1H), 8.04 (dd, $J = 8.9$, 2.7 Hz, 1H), 7.88–7.86 (m, 2H), 7.77–7.76 (m, 2H), 7.63–7.60 (m, 2H), 7.50 (t, $J = 7.5$ Hz, 4H), 7.16 (d, $J = 8.9$ Hz, 1H), 3.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.1, 150.5, 141.0, 137.9, 137.1, 134.4, 133.9, 133.3, 129.7, 129.6, 128.4, 128.0, 126.1, 124.4, 121.1, 45.7; HRMS calcd for $C_{20}H_{16}N_2O_4SNa$ $[M+Na^+]$ 403.0723; Found: 403.0733; $[\alpha]_D^{25}$ 28.92 (*c* 1.57, $CHCl_3$). **22**: Procedure B, yellow oil, yield 74%; IR: 3068, 3027, 2929, 1601, 1519, 1478, 1278, 1196 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07–8.05 (m, 2H), 7.65–7.62 (m, 2H), 7.58–7.54 (m, 2H), 7.29–7.27 (m, 1H), 7.24–7.21 (m, 1H), 6.94–6.91 (m, 1H), 3.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 139.0, 138.5, 133.7, 132.4, 129.6, 128.5, 124.4, 124.3, 121.2, 45.7; HRMS calcd for $C_{13}H_{12}N_2O_3SNa$ $[M+Na^+]$ 299.0461; Found: 299.0465; $[\alpha]_D^{25}$ 60.88 (*c* 2.27, $CHCl_3$). **24**: Procedure B, yellow oil, yield 80%; IR: 3096, 2921, 1601, 1535, 1511, 1486, 1331, 1303, 1204 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, $J = 2.7$ Hz, 1H), 8.07–8.04 (m, 3H), 7.70–7.69 (m, 1H), 7.64–7.61 (m, 2H), 7.30 (d, $J = 9.1$ Hz, 1H), 3.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.8, 143.7, 140.0, 137.4, 134.5, 130.1, 128.3, 127.1, 123.0, 120.7, 46.7; HRMS calcd for $C_{13}H_{11}N_3O_5SNa$ $[M+Na]^+$ 344.0311; Found: 344.0310; $[\alpha]_D^{25}$ −84.06 (*c* 1.23, $CHCl_3$). **26**: Procedure B, yellow oil, yield 94%; IR: 3072, 3019, 2921, 2230, 1613, 1527, 1482, 1323, 1303, 1278 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.06–8.02 (m, 2H), 7.89 (d, $J = 1.8$ Hz, 1H), 7.70–7.58 (m, 3H), 7.46–7.41 (m, 1H), 7.30 (s, 1H), 3.35 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 144.5, 143.9, 137.5, 135.3, 134.4, 130.0, 128.4, 128.3, 123.9, 117.4, 103.5, 46.5; HRMS calcd for $C_{14}H_{11}N_3O_3SNa$ $[M+Na]^+$ 324.0413; Found: 324.0418; $[\alpha]_D^{25}$ −57.85 (*c* 2.7, $CHCl_3$). **28**: Procedure B, colorless liquid, yield 72%; IR: 3072, 3027, 2929, 1597, 1491, 1450, 1331, 1290 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.05–8.01 (m, 2H), 7.61–7.50 (m, 4H), 7.23–7.22 (m, 2H), 6.93–6.90 (m, 1H), 3.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 139.0, 133.4, 132.3, 129.5, 128.4, (127.0, 126.9, 126.8, 126.7, 126.6), 124.2, 123.7, 123.2, 123.1, 122.2, 120.9, 45.2; HRMS calcd for $C_{14}H_{12}F_3NOSNa$ $[M+Na^+]$ 322.0483; Found: 322.0466; $[\alpha]_D^{25}$ −44.5 (*c* 5.77, $CHCl_3$). **32**: Procedure B, colorless solid; mp: 93–95 °C; IR: 3056, 3002, 2929, 1589, 1446, 1421, 1303, 1204 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.09–8.00 (m, 3H), 7.60–7.40 (m, 4H), 6.88–6.85 (m, 1H), 6.72 (ddd, $J = 7.3$, 5.0, 1.0 Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.9, 147.8, 140.2, 137.5, 132.9, 129.3, 127.8, 116.6, 116.0, 15.5; HRMS calcd for $C_{12}H_{12}N_2OSNa$ $[M+Na^+]$ 255.0562; Found: 255.0572; $[\alpha]_D^{25}$ −54.8 (*c* 1.77, $CHCl_3$).