JOC*Note*

Copper-Mediated Synthesis of Tertiary Diaryl Squaramides

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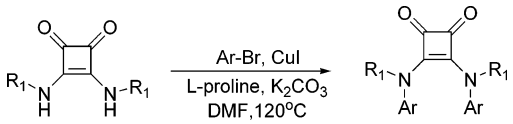
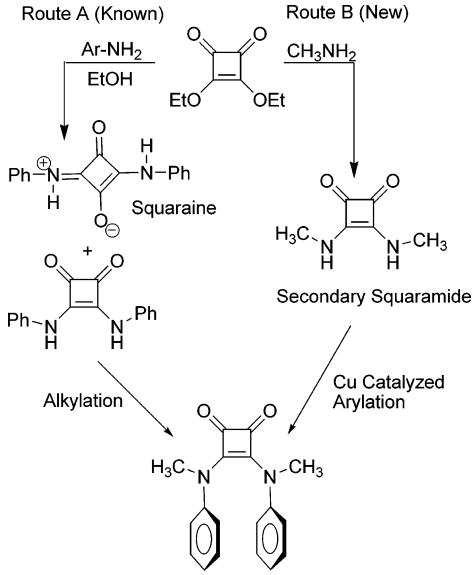


Tertiary aryl squaramides were synthesized by using copper catalyzed C−N bond-formation with L-proline as the ligand. Symmetrical diaryl squaramides could be prepared in a one-pot reaction by using excess aryl bromide with varying yields. Unsymmetrical derivatives were prepared by sequential arylation. Yields of the diarylated products were highly sensitive to steric effects.

Amide derivatives of squaric acid (squaramides) have been the focus of attention in a variety of fields ranging from medicinal chemistry to materials science.[1] Despite such widespread interest, few synthetic methods are available for this class of compounds.[2] We have recently shown that tertiary diaryl squaramides prefer the cofacial arene geometry thereby allowing for efficient through-space electronic interaction between the stacked π systems.[3] To study the electronic properties of such π-stacked arenes in greater detail, we encountered the need to prepare a variety of substituted tertiary diaryl squaramides. In our attempts to use the known[4] diamination/dialkyation strategy (Scheme 1, route A), we were frequently frustrated with the production of the 1,3-isomer (squaraine) in large amounts.[4c] To eliminate the formation of the undesired squaraine, we decided to examine the alternative diamination/diarylation route (Scheme 1, route B), with the latter step involving copper(I) mediated

SCHEME 1. Possible Routes for the Synthesis of Squaramides



C−N bond formation with an aryl bromide.[5] In this note, we describe copper-mediated synthesis of tertiary diaryl squaramides.

Examination of the literature revealed that while numerous reports of copper-mediated monoarylation of amides exist, diarylation itself has been rarely studied.[6] Furthermore, copper-mediated C−N bond formation is sensitive to steric attributes of both the amide as well as the aryl bromide.[5q] With substrates such as squaramides, given their limited conformational mobility[3,7] and the proximity of the two arylation sites,[8] this sensitivity to steric factors is likely to be even greater. Determination of

(1) (a) Onaran, M. B.; Comeau, A. B.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 10792. (b) Kinney, W. A.; Abou-Gharbia, M.; Garrison, D. T.; Schmid, J.; Kowal, D. M.; Bramlett, D. R.; Miller, T. L.; Tasse, R. P.; Zaleska, M. M.; Moyer, J. A. *J. Med. Chem.* **1998**, *41*, 236. (c) Sato, K.; Tawarada, R.; Seio, K.; Sekine, M. *Eur. J. Org. Chem.* **2004**, 2142. (d) Lim, N. C.; Morton, M. D.; Jenkins, H. A.; Bruckner, C. *J. Org. Chem.* **2003**, *68*, 9233. (e) Frontera, A.; Morey, J.; Oliver, A.; Pina, M. N.; Quinonero, D.; Costa, A.; Ballester, P.; Deya, P. M.; Anslyn, E. V. *J. Org. Chem.* **2006**, *71*, 7185. (f) Lee, C.-W.; Cao, H.; Ichiyama, K.; Rana, T. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4243. (g) Hutchings, M. G.; Ferguson, I.; Allen, S.; Zyss, J.; Ledoux, I. *J. Chem. Res., Synop.* **1998**, 244.

(2) Schmidt, A. H. *Synthesis* **1980**, 961.

(3) Muthyala, R. S.; Subramaniam, G.; Todaro, L. *Org. Lett.* **2004**, *6*, 4663.

(4) (a) Ehrhardt, H.; Huenig, S.; Puetter, H. *Chem. Ber.* **1977**, *110*, 2506. (b) Neuse, E.; Green, B. *Liebigs Ann. Chem.* **1973**, 619. (c) Neuse, E. W.; Green, B. R. *J. Org. Chem.* **1974**, *39*, 3881.

(5) Reviews on Cu-catalyzed C−N bond formation: Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1043. Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. For examples of amide arylation see: (a) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653. (b) Phillips, D. P.; Hudson, A. R.; Nguyen, B.; Lau, T. L.; McNeill, M. H.; Dalgard, J. E.; Chen, J.-H.; Penuliar, R. J.; Miller, T. A.; Zhi, L. *Tetrahedron Lett.* **2006**, *47*, 7137. (c) Barros, O. S. d. R.; Nogueira, C. W.; Stangherlin, E. C.; Menezes, P. H.; Zeni, G. *J. Org. Chem.* **2006**, *71*, 1552−1557. (d) Shen, R.; Inoue, T.; Forgac, M.; Porco, J. A. *J. Org. Chem.* **2005**, *70*, 3686. (e) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117. (f) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081. (g) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035. (h) Moriwaki, K.; Satoh, K.; Takada, M.; Ishino, Y.; Ohno, T. *Tetrahedron Lett.* **2005**, *46*, 7559. (i) Wang, S. P.; Liang, C. K.; Leung, M. K. *Tetrahedron* **2005**, *61*, 2931. (j) Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2004**, *45*, 2311. (k) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (l) Li, C. S.; Dixon, D. D. *Tetrahedron Lett.* **2004**, *45*, 4257. (m) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (n) Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475. (o) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.-Eur. J.* **2004**, *10*, 5607. (p) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (q) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (r) Dharmasena, P. M.; Oliveira-Campos, A. M. F.; Raposo, M. M. M.; Shannon, P. V. R. *J. Chem. Res., Synop.* **1994**, 296. (s) Yamamoto, T.; Kurata, Y. *Chem. Ind.* (*London*) **1981**, 737.

(6) Nandakumar, M. V. *Tetrahedron Lett.* **2004**, *45*, 1989.

(7) Rotger, M. C.; Pina, M. N.; Frontera, A.; Martorell, G.; Ballester, P.; Deya, P. M.; Costa, A. *J. Org. Chem.* **2004**, 69, 2302−2308. Thorpe, J. E. *J. Chem. Soc. B* **1968**, 435.

(8) X-ray structures of diaryl squaramides reveal the N−N distance to be 3.3 Å (see ref 3).

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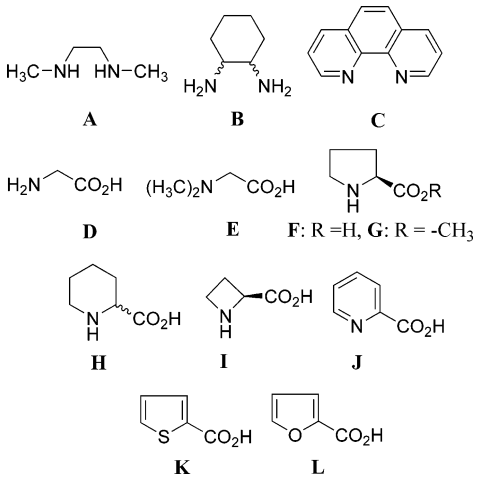


FIGURE 1. Ligands used in this study.

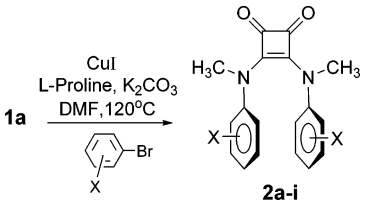
the optimal conditions for the diarylation of squaramides could, therefore, set a useful precedent for the applicability of copper-based methodology to the preparation of other sterically congested compounds.

With the goal of optimizing the reaction conditions, our initial focus was on finding the most suitable ligand using bromobenzene and dimethyl squaramide (**1a**)[4b] as the prototypical reactants with DMF as the solvent.[9] Early experiments showed that the diamine ligands (**A**−**C**),[5q] useful for amides and urea, were not effective for the arylation of squaramides. Switching to α-amino acids we found that *N*,*N*-dimethylglycine[5j] showed promise. This prompted us to examine other readily available and relatively inexpensive α-heteroatom-substituted carboxylic acids in the hope of further improving the yield. The results, which are summarized in Table 1, show two interesting trends.

First, with the exception of glycine, ligands that allow for copper chelation via nitrogen and oxygen atoms (**E**−**J**) consistently lead to higher yields compared to other ligands. Second, cyclic secondary α-amino acids **F**, **G**, **H**, and **I** give better diarylation yields. Because of its ready availability, L-proline (**F**)[5j,10] was eventually used as the ligand for all further experiments with 50 mol % copper iodide (25 mol % for each *N*-arylation). Additional experiments showed that the optimum CuI:ligand ratio was 1:1 and the best temperature for formation of the diaryl squaramide was 120 °C. Decreasing the temperature to 95 °C led to low yields while increasing the temperature to 140 °C led to complete decomposition of the products to intractable material.

The dependence of the diarylation yield on the nature and strength of the base is also interesting. For example, while the reaction worked with K_2CO_3 use of K_3PO_4 did not lead to any product formation. Presumably, with a stronger base, facile deprotonation[11] of dimethyl squaramide or the copper amidates[12] **3** and **4** (Figure 2) could lead to an accumulation of multiply ligated species[5q,12a] such as **5** and **6** if the rate of arylation is slower than the rate of deprotonation.[13]

TABLE 1. Reaction Optimization for Diarylation[a]



entry	L	base	T[b] (°C)	CuI:L	yield[c] (%)
1		K_2CO_3	120		7
2	A	K_2CO_3	120	1:1	17
3	B[d]	K_2CO_3	120	1:1	26
4	C	K_2CO_3	120	1:1	27
5	D	K_2CO_3	120	1:1	<5
6	E	K_2CO_3	120	1:1	45
7	G	K_2CO_3	120	1:1	60
8	F	K_2CO_3	120	1:1	65
9	F	K_2CO_3	120	1:2	30
10	F	K_2CO_3	120	2:1	28
12	F	K_2CO_3	95	1:1	21
13	F	K_2CO_3	140	1:1	<5
14	F	K_3PO_4	120	1:1	0
15	F	Cs_2CO_3	120	1:1	0
16	F	Na_2CO_3	120	1:1	20
17	H[e]	K_2CO_3	120	1:1	60
18	I	K_2CO_3	120	1:1	63
19	J	K_2CO_3	120	1:1	50
20	K	K_2CO_3	120	1:1	31
21	L	K_2CO_3	120	1:1	27

[a] Reaction conditions: squaramide (1 mmol), PhBr (3 mmol), CuI (0.5 mmol), ligand (0.5 mmol), K_2CO_3 (2.5 mmol), DMF 1 mL; time 18 h. [b] Reaction temperature. [c] Isolated yields after column chromatography. [d] Cis−trans mixture. [e] Racemic.

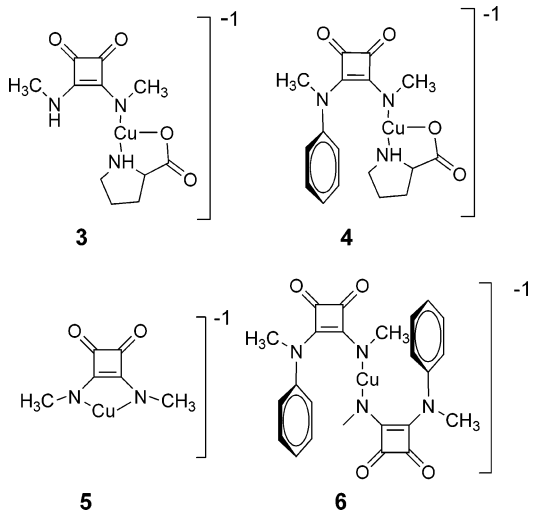


FIGURE 2. Putative copper amidates.

Using the optimized conditions for bromobenzene, substituent effects were next examined (Table 2). With *p*-chlorobromobenzene, the C−Cl bond is unaffected and exclusive insertion into the C−Br bond is observed. Overall, product yields with electron-donating groups are significantly higher than those with

(9) The poor solubility of **1a** in dioxane or toluene restricted us to DMF.

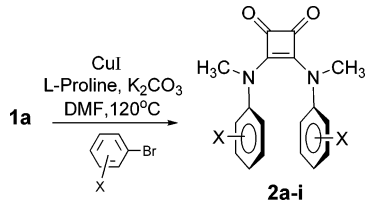
(10) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

(11) Squaramides could be highly acidic for reasons similar to that of squaric acid (see: Smith M. B.; March J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001; p 70).

(12) (a) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120. (b) Yamamoto, T.; Ehara, Y.; Kubota, M.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1299.

(13) The importance of the rate of arylation matching the rate of deprotonation has been noted earlier by Buchwald and co-workers (see ref 5q).

TABLE 2. Substituent Effects on Diarylation[a]



entry	X	product	yield[b] (%)
1	H	**2a**	65
2	4-Cl	**2b**	44
3	2-CH_3	**2c**[c]	20
4	4-CH_3	**2d**	70
5	4-$N(CH_3)_2$	**2e**	55
6	4-CO_2CH_3	**2f**	10[d]
7	3- CO_2CH_3	**2g**[c]	21[d]
8	4-$CH_2CO_2C_2H_5$	**2h**	45
9	4-NO_2	**2i**	0

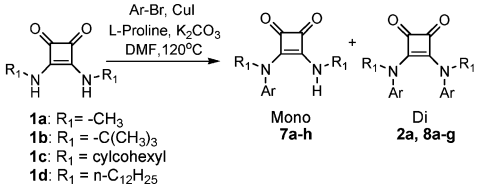
[a] Reaction conditions: squaramide (1 mmol), ArBr (3 mmol), CuI (0.5 mmol), L-proline (0.5 mmol), K_2CO_3 (2.5 mmol), DMF 1 mL; time 18 h. [b] Isolated yields after column chromatography. [c] Only the anti EE conformer was detectable by NMR. [d] Reaction was stopped after 3 h.

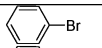
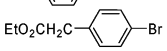
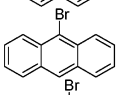
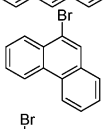
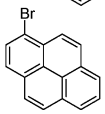
electron-withdrawing groups. The problem with the latter substituents appears to be thermal instability of the squaramide product rather than a lack of reaction.[14] For example, with a nitro substituent decomposition to polymeric material was so rapid even at 90 °C that we were unable to isolate any identifiable product. With a methoxycarbonyl group at the para or meta position, a small amount of the diarylated material could be isolated by shortening the reaction time. With 2-bromotoluene, the diarylated product was obtained in significantly lower yields compared to 4-bromotoluene, clearly indicating adverse steric effects in the former.

The sensitivity of the diarylation reaction to steric factors is further evident from Table 3. Investigating the effects of structural variation on the squaramide reactant[14] we found that while diarylated products are obtained with linear unbranched (**1a** and **1d**) alkyl groups, any branching on the carbon attached to the nitrogen atoms leads exclusively to monoarylation in high yields. For example, with cyclohexyl or *tert*-butyl groups only the monoaryl squaramides **7b** and **7c** were obtained in 85% and 96% yield, respectively, despite using excess bromobenzene and prolonged heating.

With polycyclic aryl bromides, the position of the bromine atom relative to the ring junction appears to be more important in determining whether the diarylated product is obtained.[15] When the C−Br bond is flanked by two ring junctions, as in 9-bromoanthracene, only the monoarylated product (**7f**) is obtained. In comparison, 9-bromophenanthrene yielded the diaryl product **8f**. With the larger 1-bromopyrene, however, only the monoarylated product was obtained. Repeated attempts to obtain the dipyrenyl squaramide even in a microwave reactor[16] at 140 °C were not successful. Therefore, diarylation is clearly dependent on the steric attributes of the reactants. This is likely

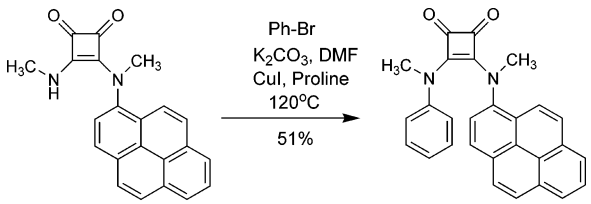
TABLE 3. Variation of the Steric Bulk of the *N*-Alkyl Group and Aryl Ring Size[a]



Entry	#	Ar-Br	Product Yield[b] (%) Mono +Di
1	**1a**		**7a** (12)+**2a** (65)
2	**1b**		**7b** (96)+**8a** (0)
3	**1c**		**7c**(85)+ **8b**(0)
4	**1d**		**7d** (35)+ **8c** (18)
5	**1a**		**7e** (10)+**8d**(35)[b]
6	**1a**		**7f** (12) +**8e** (0)
7	**1a**		**7g** (30)+**8f** (14)[c]
8	**1a**		**7h** (55)+**8g** (0)

[a] Reaction conditions: squaramide (1 mmol), ArBr (3 mmol), CuI (0.5 mmol), L-proline (0.5 mmol), K_2CO_3 (2.5 mmol), DMF 1 mL; time 18 h. [b] Isolated yields after column chromatography. [c] Mixture of syn and anti isomers.

SCHEME 2. Synthesis of Unsymmetrical Squaramides



attributable to the proximity of the reaction sites and the preference of tertiary diaryl squaramides for the cofacial arene conformation[3] imposing severe steric constraints during C−N bond formation.

A particularly useful feature of the copper-catalyzed arylation is that it can be used to synthesize unsymmetrical squaramides. As an illustrative example, we show (Scheme 2) the conversion of **7h** to the mixed squaramide **9** by reaction with bromobenzene. Synthesis of such unsymmetrical squaramides with very different aryl ring sizes and electronic characteristics could be useful in the design of new squaramide based sensors and switches.[17]

In summary, a new synthetic approach to symmetrical and unsymmetrical tertiary squaramides is described with use of

(14) The squaramides **1b**−**d** respectively were prepared as reported in: Schmidt, A. H. *Synthesis* **1980**, 961. Frauenhoff, G. R.; Takusagawa, F.; Busch, H. *Inorg. Chem.* **1992**, *31*, 4002. Hutchings, M. G.; Ferguson, I.; Allen, S.; Zyss, J.; Ledoux, I. *J. Chem. Res., Synop.* **1998**, *5*, 244.

(15) Bacon, R. G. R.; Karim, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 272.

(16) (a) He, H.; Wu, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 3385. (b) Yadav, L. D. S.; Yadav, B. S.; Rai, V. K. *Synthesis* **2006**, 1868.

(17) Callan, J. F.; de Silva, A. P.; Magri, D. C. *Tetrahedron* **2005**, *61*, 8551.

copper-mediated diarylation with aromatic bromides. This study sets the stage for the exploration of through-space electronic interactions[18] in π-stacked arenes with use of the unique squaric acid scaffold. Studies in this direction are ongoing in our laboratory and will be reported in due course.

Experimental Section

Typical Procedure for Diarylation. To a 5 mL, round-bottomed flask was added copper iodide (95 mg, 0.5 mmol), L-proline (58 mg, 0.5 mmol), potassium carbonate (345 mg, 2.5 mmol), and anhydrous DMF (1 mL). The mixture was stirred at room temperature under nitrogen atmosphere for 20 min. Bromobenzene (471 mg, 3 mmol) and 3,4-bis(methylamino)cyclobut-3-ene-1,2-dione (140 mg, 1 mmol) were then added and the reaction temperature was increased to 120 °C. After 18 h, the reaction mixture was cooled to room temperature, diluted with ethylacetate (25 mL), filtered, and concentrated. The residue was then chromatographed on silica gel with hexane:ethyl acetate (3:2) as the eluent to give **2a**[3,4a] in 65% yield. ^{1}H NMR ($CDCl_3$): δ 7.02 (4H, t, J = 7.6 Hz), 6.89 (2H, t, J = 7.2 Hz), 6.61 (4H, d, J = 7.6 Hz), 3.70 (6H, s) ppm. ^{13}C NMR ($CDCl_3$): δ 186.7, 167.6, 142.8, 128.8, 125.0, 121.2, 39.1 ppm.

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Supporting Information Available: Experimental procedures and characterization data for all compounds and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070393L

(18) (a) Lewis, F. D.; Kurth, T. L.; Delos Santos, G. B. *J. Phys. Chem. B* **2005**, *109*, 4893. (b) Wolf, C.; Mei, X. *J. Am. Chem. Soc.* **2003**, *125*, 10651.