COPPER(II) BROMIDE–CATALYZED C-C/C-N
BOND-FORMING REACTIONS: SYNTHESIS OF
PYRROLE-INCORPORATED TRIARYLMETHANES

H. Surya Prakash Rao, A. Veera Bhadra Rao, and
Sivakumar Shanmugam
Department of Chemistry, Pondicherry University, Pondicherry, India

GRAPHICAL ABSTRACT

Abstract We have achieved a facile copper(II) bromide–catalyzed synthesis of 2,3,4-
trisubstituted pyrrole incorporated into unsymmetrical triarylmethanes through direct
replacement of hydroxyl group in the pyrrolyl phenyl methanol with electron-rich
aromatic and heteroaromatic compounds. The newly developed method has been applied
to a facile synthesis of a C2 symmetric bis-triarylmethane in which the two
triarylmethanes were bridged through piperazine. The copper(II) bromide catalysis led to
C-C bond formation at the C(5) position when the reacting partner was imidazole. In
contrast, C-N bond formation took place with benzimidazole or 2-methylbenzimidazole.

Keywords C-C bond; C-N bond; copper; triarylmethanes

INTRODUCTION

Triarylmethanes are a group of organic molecules that have three aryl groups
appended to the central carbon atom. This group has diverse applications as dyes
(e.g., malachite green), drugs (e.g., turbomycin), and pH indicators (e.g., cresol
red).[1] Incorporating heteroaromatic rings in place of normal aromatic rings
makes the triarylmethanes much different from the parent molecules.[2] For example,
when heteroaromatic rings such as pyrrole, indole, and imidazole are placed in the
network of triarylmethanes, the resulting molecules exhibit enhanced biological
activity.[2a]
Triarylmethanes are mostly synthesized by treatment of electrophilic reagents such as triethyl orthoformate or arene aldehydes with various arene nucleophiles in the presence of Lewis acids. Generally, only symmetrical triarylmethanes result by application of these methods. Although synthesis of some unsymmetrical triarylmethanes has been achieved through direct replacement of benzylic hydroxyl group with arene nucleophiles, the reactions require a stiochometric amount of Lewis acid. In view of the recent developments and in continuation of our work on copper-mediated C-C bond-forming reactions, we disclose here a new method for the synthesis of unsymmetrical triarylmethanes. We now show that facile and direct replacement of free hydroxyl group in diaryl methanols with arene nucleophiles takes place under copper(II) bromide catalysis.

DISCUSSION

We have recently described a convenient method for the synthesis of pyrrolyl aryl ketones, for example, 1 from ζ-oxoketene dithioacetals and tosylmethyl isocyanide (TOSMIC). The reaction involved 1,3-dipolar cycloaddition of TOSMIC to ζ-oxoketene dithioacetals in the presence of sodium hydride. The pyrrolyl aryl ketone 1 was reduced to pyrrolyl phenyl methanol 2 with sodium borohydride to furnish the secondary alcohol 2 in 86% yield (Scheme 1). We targeted replacement of the hydroxy group in 2 with aryl groups to achieve synthesis of unsymmetrical triarylmethanes of the type 3.

We selected synthesis of unsymmetrical triarylmethane 3a as a test case for optimization of reaction conditions (Scheme 2, Table 1). Initially we conducted a reaction between pyrrolyl phenyl methanol 2 and N,N-dimethylaniline 4a using Cu(OTf)2 in DCE reflux and the reaction provided triarylmethane 3a in moderate 24% yield (Table 1, entry 1). For improving the reaction yield, we screened different copper(II) salts such as CuBr2 (10 mol%, 92%, entry 2), CuBr2 (5 mol%, 74%, entry 3), CuCl2 (52%, entry 4), and Cu(OAc)2 (no reaction, entry 5) in DCE reflux. As an alternative to copper(II) catalysts, we tried InCl3 (soft Lewis acid, 10 mol%, 52%, entry 6), ZnBr2 (soft Lewis acid, no reaction, entry 7), and FeCl3 (relatively hard Lewis acid, no reaction, entry 8), but they were not better than CuBr2. Thus, we concluded that CuBr2 (10 mol%) in DCE reflux was found to be the best catalyst for the transformation. Formation of 3a was assured by 1H, 13C, and DEPT-135 NMR spectroscopic data. Characteristic singlet at δ 5.46 ppm assignable to methine hydrogen in its 1H NMR spectrum of 3a along with the methine carbon signal at δ 47.0 ppm in 13C NMR spectrum confirmed the assigned structure.

Scheme 1. Synthesis of hydroxy compound 2 from corresponding ketone 1.
With optimized conditions in hand, we repeated the reaction of alcohol 2 with two electron-rich arene nucleophiles such as \(N,N\)-diethylaniline and \(\beta\)-napthol to yield corresponding triarylmethanes 3b and 3c in good yield (Scheme 2). Next, we extended the strategy with an aim to incorporate heteroaromatic moities such as pyrrole, indole, and imidazole into unsymmetrical triarylmethane framework. Each of these reactions worked well to furnish corresponding triarylmethanes 3d–f. As expected, for pyrrole the electrophilic substitution took place on C(2), i.e., \(\alpha\) position to provide 3d [for indole it was on C(3)] and \(\beta\) position to provide 3e [for imidazole the substitution was on C(4) position to provide 3f]. Regiochemistry of the substitutions was ensured from NMR spectral data.

Next, we planned for the synthesis of bis-triarylmethane 3g by reacting 2 equiv of alcohol 2 with 1,4-diphenylpiperzine 4g in the presence of 10 mol% of CuBr₂ in

**Table 1.** Optimization of reaction conditions for synthesis of pyrrole incorporated triarylmethanes with different catalysts

| Entry | Catalyst | Mol (%) | Time (h) | Yield (%) |
|-------|----------|---------|----------|-----------|
| 1     | Cu(OTf)₂ | 10      | 6        | 24        |
| 2     | CuBr₂    | 10      | 2        | 92        |
| 3     | CuBr₂    | 05      | 2        | 74        |
| 4     | CuCl₂    | 10      | 6        | 52        |
| 5     | Cu(OAc)₂· H₂O | 10 | 6 | nr |
| 6     | InCl₃    | 10      | 6        | 52        |
| 7     | ZnBr₂    | 10      | 6        | nr        |
| 8     | FeCl₃· 6H₂O | 10 | 6 | nr |

*Note.* nr, no reaction.
DCE reflux. The reaction between 2 and 4 was smooth to furnish C2-symmetric bis-triarylmethane 3g in 78% yield.

In continuation of this study we treated hydroxy compound 2 with benzimidazole under copper(II) bromide catalysis to incorporate the benzimidazole motif into the unsymmetrical triarylmethanes 3. Benzimidazole 4h has two possible nucleophilic sites, namely N(1) and C(2). The reaction of 2 with benzimidazole was regioselective to provide 3h exclusively in 89% yield through CN bond formation. Generation of 3h was ensured from the NMR spectra; the 1H NMR spectrum exhibited a singlet at 6.63 ppm for methine hydrogen. This signal got downfield shifted from about 5.5 ppm for 3a owing to attached electronegative nitrogen atom. Finally, we treated 2 with 2-methylbenzimidazole 4i to obtain triarylmethane 3i in 83% yield via C-N bond formation.

Mechanistically, substitution of the hydroxyl group in 2 could go through generation of copper-bound carbocation in the first step. Quenching of the soft carbocation in the second step by aryl groups at their respective electron-rich carbon/nitrogen centers leads to triarylmethanes. Copper(II) bromide appears to be most suitable catalyst for both the steps.

**CONCLUSION**

In conclusion, we have demonstrated a facile method for synthesis of pyrrole-incorporated unsymmetrical triarylmethanes via C-C or C-N bond formation under copper(II) bromide catalysis. The method is general and applicable to synthesis of a variety of triarylmethanes.

**EXPERIMENTAL**

**Synthesis of N,N-Dimethyl-4-((4-(methylthio)-5-tosyl-1H-pyrrol-3-yl) (phenyl)methyl)aniline 3a**

CuBr₂ (4 mg, 10 mol%) and N,N-dimethylaniline 4a (19 mg, 0.16 mmol) were added in sequence to a stirred solution of (4-(methylthio)-5-tosyl-1H-pyrrol-3-yl)
(phenyl)methanol \(2\) (60 mg, 0.16 mmol) in 2 mL DCE at room temperature. The reaction mixture was allowed to reflux for 2h, by which time the reaction was complete (measured by thin-layer chromatography, TLC). The reaction mixture was diluted with dichloromethane (DCM, 20 mL), and the resulting solution was washed with water (2 \( \times \) 20 mL) and brine solution (20 mL). The organic layer was separated and dried over anhydrous \(\text{Na}_2\text{SO}_4\). Evaporation of DCM solvent under reduced pressure resulted in crude product, which was subjected to column chromatography using silica gel (100–200 mesh) and solution of EtOAc in hexanes (8:2) to provide \(N,N\)-dimethyl-4-((4-(methylthio)-5-tosyl-1\(H\)-pyrrol-3-yl)(phenyl)methyl)aniline \(3a\) in 92\% yield (71 mg) as a white solid mp 152 °C; \(R_F = 0.4\) (hexanes/EtOAc 8:2). IR (KBr): 3427, 3297, 2922, 1707, 1596, 1542, 1443, 1307, 1225, 1142, 969, 810, 754, 696, 595 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\) + CCl\(_4\); 1:1) \(\delta\) 9.88 (s, 1H), 7.94–7.92 (d, \(J = 8.0\) Hz, 2H), 7.28–7.08 (m, 5H), 6.93–6.90 (d, \(J = 6.6\) Hz, 2H), 6.60–6.56 (d, \(J = 8.8\) Hz, 2H), 5.46 (s, 1H), 2.88 (s, 6H), 2.39 (s, 3H), 1.76 (s 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\) + CCl\(_4\); 1:1): \(\delta\) 149.2 (C), 144.6 (C), 143.9 (C), 139.1 (C), 135.3 (C), 131.9 (C), 130.7 (C), 129.6 (2 × CH), 129.0 (CH), 128.3 (CH), 127.9 (CH), 126.1 (CH), 121.7 (CH), 119.0 (C), 112.7 (CH), 47.1 (CH), 40.8 (CH\(_3\)), 21.8 (CH\(_3\)), 20.4 (CH\(_3\)); HRMS (ESI\(^{+}\)) calcd. for \(C_{27}H_{29}N_2O_2S_2\) (M + H) 477.1670; found 477.1672.

**ACKNOWLEDGMENT**

We thank CIF, PU for spectroscopic facilities.

**FUNDING**

H. S. P. thanks the University Grants Commission, SAP, Department of Science and Technology Funding for Infrastructure in Science and Technology, for financial support. A. V. R. thanks the Council on Scientific and Industrial Research–NET for a research fellowship.

**SUPPLEMENTAL MATERIAL**

Full experimental details, \(^1\)H and \(^{13}\)C NMR spectra, and DEPT spectra of all compounds for this article can be accessed on the publisher’s website.

**REFERENCES**

1. (a) Mondal, S.; Panda, G. *RSC Adv.* **2014** 4, 28317–28358; (b) Nair, V.; Thomas, S.; Smitha, C. M.; Abhilash, K. G. *Tetrahedron* **2006**, 62, 6731–6747; (c) Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev.* **2003**, 32, 170–180 (d) Gillespie, D. E.; Brady, S. F.; Bettermann, A. D.; Cianciotto, N. P.; Liles, M. R.; Rondon, M. R.; Clardy, J.; Goodman, R. M.; Handelsman, J. *Appl. Environ. Microbiol.* **2002**, 68, 4301–4306; (e) Muthyala, R.; Katritzky, A. R.; Lan, X. F. *Dyes Pigm.* **1994**, 25, 303–324.

2. (a) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorganic Med. Chem. Lett.* **2008**, 18, 289–292; (b) Al-Qawasneh, R. A.; Lee, Y.; Cao, M.-Y.; Gu, X.; Vassilakos, A.; Wright, J. A.; Young, A. *Bioorg. Med. Chem. Lett.* **2004**, 14, 347–350; (c) Kandela, I. K.; Bartlett, J. A.; Indig, G. L. *Photochem. Photobiol. Sci.* **2002**, 1, 309–314.
3. (a) Leng, Y.; Chen, F.; Zuo, L.; Duan, W. *Tetrahedron Lett.* 2010, 51, 2370–2373; (b) Prakash, G. K. S.; Panja, C.; Shakham, A.; Shah, E.; Mathew, T.; Olah, G. A. *J. Org. Chem.* 2009, 74, 8659–8668; (c) Li, Z.; Duan, Z.; Kang, J.; Wang, H.; Yu, L.; Wu, Y. *Tetrahedron* 2008, 64, 1924–1930; (d) Nair, V.; Abhilash, K. G.; Vidy, N. *Org. Lett.* 2005, 7, 5857–5859.

4. Werbel, L. M.; Elslager, E. F.; Pearlman, W. M. *J. Org. Chem.* 1964, 29, 967–968.

5. (a) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* 2007, 9, 2373–2375; (b) Yu, J.; Kuwano, R. *Org. Lett.* 2008, 10, 973–976; (c) Thirupathi, P.; Kim, S. S. *Tetrahedron* 2010, 66, 2995–3003; (d) Hikawa, H.; Suzuki, H.; Azumaya, I. *J. Org. Chem.* 2013, 78, 12128–12135; (e) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* 2013, 135, 3303–3306; (f) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* 2013, 135, 3307–3310; (g) Tabuchi, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* 2014, 79, 5401–5411; (h) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. *J. Am. Chem. Soc.* 2014, 136, 5828–5831; (i) Nambo, M.; Crudden, C. M. *Angew. Chem. Int. Ed.* 2014, 53, 742–746; (j) Nambo, M.; Crudden, C. M. *ACS Catal.* 2015, 5, 4734–4742.

6. (a) Rao, H. S. P.; Rao, A. V. B. *Eur. J. Org. Chem.* 2014, 3646–3655; (b) Rao, H. S. P.; Rao, A. V. B. *J. Org. Chem.* 2015, 80, 1506–1516.

7. Rao, H. S. P.; Sivakumar, S. *Beilstein J. Org. Chem.* 2007, 3, 30–35.

8. Lu, J.; Yang, B.; Bai, Y. *Synth. Commun.* 2002, 32, 3703–3709.

9. (a) Joule, J.; Mills, K. *Heterocyclic Chemistry*; John Wiley & Sons, London, 2010; pp. 456–461; (b) Grimmett, M. R In Comprehensive Heterocyclic Chemistry I: Imidazoles and Their Benzo Derivatives: Reactivity; A. R. Katritzky (Eds.); 1984; Vol. 5, pp. 375–456; (c) Grimmett, M. R., In Comprehensive Heterocyclic Chemistry II: Imidazoles; A. R. Katritzky (Eds.); 1996; Vol. 3, pp. 79–220; (d) Xi, N.; Huang, Q.; Liu, L. In Comprehensive Heterocyclic Chemistry III; A. R. Katritzky (Eds.); Pergamon: Oxford, UK, 2008; Vol. 4, pp. 143–364.