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Promotion of Reaction of N-H Bonds with Triarylbismuth and Cupric Acetate

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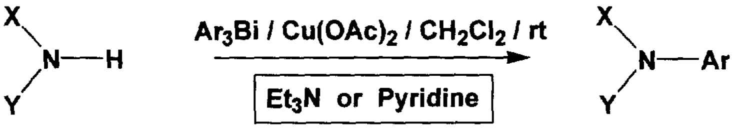
Abstract: Arylation of a diverse group of N-H containing compounds at room temperature with triarylbismuth and cupric acetate in the presence of a tertiary amine promoter, such as triethylamine or pyridine, is described. This mild and highly efficient procedure, which is based on Barton's earlier work on the arylation of amines, can be applied to amides, imides, ureas, carbamates, and sulfonamides. Copyright © 1996 Elsevier Science Ltd

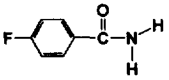
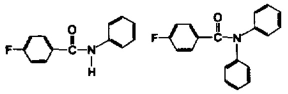
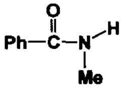
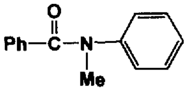
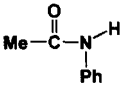
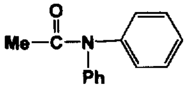
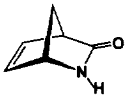
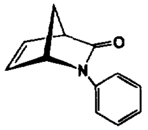
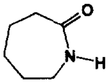
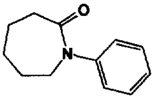
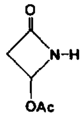
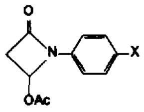
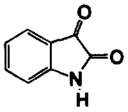
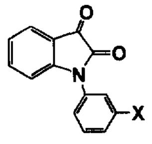
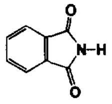
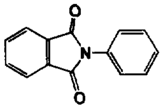
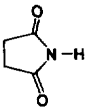
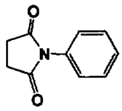
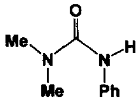
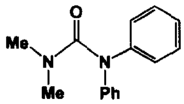
Arylbismuth reagents have been shown by Barton to arylate aliphatic and aromatic amines in the presence of metallic copper or a copper(II) salt under mild conditions.[1, 2, 3] While such methodology has found utility in the synthesis of anilines from basic amines,[4, 5] and in the arylation of indoles,[6] application to less reactive N-H bonds has not been fully explored.[3, 7] The few reported attempts of arylating amides and imides using the organobismuth alone, or in the presence of copper, either failed completely or gave very unsatisfactory yields.[1a, 8] Almost all of these reactions require the use of high temperatures, very basic conditions, and long reaction time.[8, 9, 10]

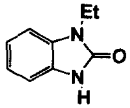
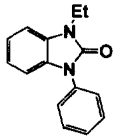
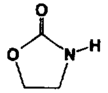
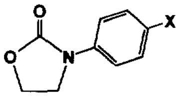
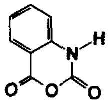
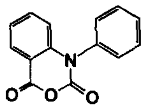
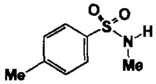
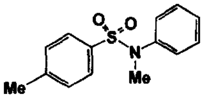
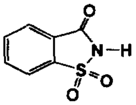
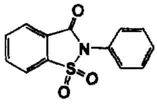
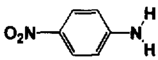
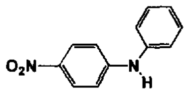
We wish to report here that many classes of N-H containing compounds can be efficiently arylated with Ar_3Bi and cupric acetate *in the presence of a tertiary amine promoter such as triethylamine or pyridine*. With this modification, the bismuth-copper arylation can now be applied to amides, ureas, carbamates, imides, and sulfonamides, allowing the reaction to proceed at room temperature in good to excellent yields (see Table). As evidenced by our results, an amine promoter has a remarkable effect in these arylation reactions: no product is observed in its absence in the case of 4-fluorobenzamide, and it also significantly improves the yield in the phenylation of 4-nitroaniline (entries 1 and 16). Even a catalytic amount (10%) of the amine is sufficient to promote arylation, although using larger quantities seems to produce a higher yield in some instances (entries 7, 10, and 13).



X, Y = COR, CO_2R, $CONR_2$, SO_2R, R, H (R = alkyl and aryl)

Table: Examples of Tertiary Amine-promoted N-arylation with Triarylbismuth[11] and Cupric Acetate.[12]

Entry	Substrate	Product[a]	Promoter	Bi : Cu : P / t[b]	Yield[c]
	Amides				
1			none	1.2 : 1 : 0 / 72	0%
		4.4 : 1.0	Pyridine	1.2 : 1 : 1 / 31	83%
		1.1 : 1.0	Et_3N	1.2 : 1 : 1 / 31	71%
2			Et_3N	2 : 1.5 : 1.5 / 40	81%
			Pyridine	2 : 1.5 : 1.5 / 48	44%
3			Et_3N	1.1 : 1 : 0.5 / 24	76%
			Pyridine	1.1 : 1 : 0.5 / 24	74%
4			Et_3N	2 : 1.5 : 1.5 / 24	100%
5			Et_3N	1.1 : 1 : 1 / 24	93%
6			X=H, Et_3N	2 : 1.5 : 1.5 / 24	75%
			X=F, Et_3N	2 : 1.5 : 1.5 / 5	93%
			X=Cl, Et_3N	2 : 1.5 : 1.5 / 4	85%
7			X=H, Et_3N	1 : 1 : 1 / 40	87%
			X=H, Et_3N	1 : 1 : 0.1 / 40	80%
			X=H, Pyridine	1 : 1 : 1 / 48	71%
			X=F, Et_3N	1 : 1 : 1 / 20	65%
	Imides				
8			Pyridine	1.1 : 1 : 1 / 48	99%
			Et_3N	1.1 : 1 : 1 / 72	63%
9			Pyridine	1.1 : 1 : 1 / 24	98%
			Et_3N	1.1 : 1 : 1 / 24	72%
	Ureas				
10			Et_3N	1.2 : 1 : 1 / 36	77%
			Et_3N	1.2 : 1 : 0.1 / 36	36%

11			Et_3N	1.2 : 1: 1 / 23	100%
	Carbamates				
12			X=H, Et_3N X=OCF_3, Pyr.	2 : 1.5 : 1.5 / 24 1 : 1 : 1 / 24	94% 76%
13			Pyridine Pyridine Et_3N	2 : 1 : 1 / 42 2 : 1 : 0.1 / 45 2 : 1.5 : 1.5 / 40	64% 55% 20%
	Sulfonamides				
14			Pyridine Et_3N	2 : 1.5 : 1.5 / 6 2 : 1.5 : 1.5 / 6	99% 82%
15			Pyridine Et_3N	2 : 1.5 : 1.5 / 27 2 : 1.5 : 1.5 / 27	82% 63%
	Aniline				
16			none Et_3N Et_3N	1.2 : 0.5 : 0 / 24 1.2 : 0.5 : 1 / 24 1.2 : 0.5 : 0.1 / 24	6% [d] 80% 94%

a) The spectral data for the new compounds were in accord with the structures assigned.
b) Bi : Cu : P / t = molar equivalents of Ar_3Bi : $Cu(OAc)_2$: amine promoter / reaction time (hr).
c) Isolated yields. No optimization was attempted in most cases.
d) From Reference 1b.

The difference between using Et_3N or pyridine as a promoter is also noteworthy. It appears that Et_3N is better at promoting amide arylation, whereas pyridine is more effective with imides and sulfonamides (entries 2, 7, 8, 9, 14, and 15). However, with a primary amide, pyridine gives more of the mono-arylated product and a slightly better yield (entry 1). The high efficiency in the case of isatin N-arylation (entry 7) and the direct N-phenylation of isatoic anhydride under mild conditions (entry 13) are considerable improvements over a previous report.[13] While the exact role the tertiary amine plays in promoting these reactions needs further investigation, one possibility is that it serves to enhance the solubility and reactivity of cupric acetate and the various copper species involved in product formation.[14] Alternatively it may also help to buffer the reaction since acetic acid is presumably generated as a byproduct. It is likely the explanation is a combination of different factors, including the ones suggested here.

In summary, we have demonstrated that a tertiary amine promoter can greatly enhance the scope and the yield of Barton's copper(II)-mediated organobismuth N-arylation. As shown by our results, the reaction is broadly applicable to a large variety of substrates, and is also very tolerant to many highly sensitive functionalities. Because of its mild conditions and high yields, this arylation is ideally suited for preparation of analogs. Work on futher improving the process is underway and will be reported in due course.

General Procedure for Arylation: A slurry of the substrate, triarylbismuth (1-2 eq.), anhydrous $Cu(OAc)_2$ (1-1.5 eq.), the tertiary amine (0.1-1.5 eq.) in methylene chloride (~2.5 ml/mmol of substrate) was stirred at room temperature for 6-48 hr.[15] The products were isolated by direct flash column chromatography of the crude reaction mixture with preabsorption on silica gel.

Acknowledgement : I am grateful to Rebecca L. Lowe and Kevin L. Monaco for their technical assistance.

References and Notes

1. (a) Barton, D.H.R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1986**, *27*, 3615-3618; (b) Barton, D.H.R.; Finet, J.-P.; Khamsi, *Tetrahedron Lett.* **1987**, *28*, 887-890.
2. Barton, D.H.R.; Ozbalik, N.; Ramesh, M. *Tetrahedron Lett.* **1988**, *29*, 857-860.
3. For an overview, see: Finet, J.-P. *Chem. Rev.* **1989**, *89*, 1487-1501.
4. Barton, D.H.R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1989**, *30*, 937-940.
5. Banfi, A.; Bartoletti, M.; Bellora, E.; Bignotti, M.; Turconi, M. *Synthesis*, **1994**, 775-776.
6. Barton, D.H.R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1988**, *29*, 1115-1118.
7. The efficiency of arylation with the Ar_3Bi / $Cu(OAc)_2$ system has been shown by Barton to be highly dependent on the basicity of the amine substrate, e.g., *n*-butylamine gave a good yield of the N-phenylated derivatives but *p*-nitroaniline reacted poorly. See ref. 1b.
8. Barton, D.H.R.; Finet, J.-P.; Motherwell, W.B.; Pichon, C. *J. Chem. Soc., Perkin Trans. I,* **1987**, 251-259.
9. Barton, D.H.R.; Blazejewski, J.-C.; Charpiot, B.; Lester, D.J.; Motherwell, W.B.; Barros Papoula, M.T. *J. Chem. Soc., Chem. Commun.* **1980**, 827-829.
10. Akhtar, M.S.; Brouillette, W.J.; Waterhous, D.V. *J. Org. Chem.* **1990**, *55*, 5222-5225.
11. Triphenylbismuth was obtained commerically. Other triarylbismuth reagents were prepared from the corresponding arylmagnesium halide and $BiCl_3$. See ref. 5 for examples and a typical procedure. For a discussion on preparation of various triarylbismuth compounds, see: Barton, D.H.R.; Bhatnagar, N.Y.; Finet, J.-P.; Motherwell, W.B. *Tetrahedron*, **1986**, *42*, 3111-3122.
12. Preliminary results indicate that other Cu(II) salts, both the anhydrous and hydrated form, may also be used in place of $Cu(OAc)_2$. Examples are: $CuBr_2$, $CuCl_2$, $Cu(SO_2Ph)_2$, $Cu(OCOPh)_2$, and $Cu(NO_3)_2$. This is in contrast to ref. 1b where only $Cu(OAc)_2$ and $Cu(OCOCF_3)_2$ were reported to be effective. The Cu(II) salts found to be not effective were: CuF_2, CuO, and $CuSO_4$.
13. Coppola, G.M. *J. Heterocyclic Chem.*, **1987**, *24*, 1249-1251.
14. For a discussion on the reaction mechanism of the Cu-mediated bismuth N-arylation, see reference 1b.
15. The progress of the reaction could be monitored by TLC as well as by the color change from the initial deep blue to turquoise green, with the concomitant precipitation of grayish Cu(I) salt. Additional amounts of Ar_3Bi and $Cu(OAc)_2$ could be added during the course of the reaction to ensure complete conversion of the substrate.

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