Tetrahedron Letters,Vol.29,No.10,pp 1115-1118,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

COPPER CATALYSED PHENYLATION OF INDOLES BY TRIPHENYLBISMUTH BIS-TRIFLUOROACETATE

Derek H. R. Barton[a,b], Jean-Pierre Finet[a,c], and Jamal Khamsi[a,b]

a. Institut de Chimie des Substances Naturelles, C.N.R.S.,
91198 Gif-sur-Yvette, France

b. Department of Chemistry, Texas A&M University, College
Station, Texas 77843, U.S.A.

c. Laboratoire de Chimie Organique B, Faculté des Sciences,
St. Jérôme, 13397 Marseille Cedex 13, France

Abstract: Indoles are C(3)- or N-phenylated by triphenylbismuth bis-trifluoroacetate under copper catalysis. C(3)-Phenyl derivatives are obtained with C(3)-unsubstituted indoles and N-phenyl derivatives with C(3)-substituted indoles.

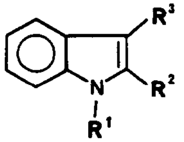
In previous communications, we have reported the arylation of various hydroxyl and nitrogen containing substrates by $Ph_3Bi(OCOR)_2$ reagents 1 and 2 in the presence of copper catalysts 3-5[1-4]. Organobismuth reagents present similarities in their general reactivity with diaryliodonium[5] and organolead[6] derivatives. However, ordinary enamines react with iodonium[7] and lead[8] compounds, but not with bismuth^{V} reagents. The indole nucleus, found in many biologically important natural products, is characterized by an ambident enaminic type reactivity[9]. We extended our studies of the reactivity of pentavalent organobismuth reagents to the arylation of indolic compounds. In previous papers, we have already described the non-catalyzed phenylation of indole 8 to mono- or di-phenyl derivatives 9-11[10], and the phenylation of 3-methylindole 12 to 13, all under basic conditions[11]. We now report our results on the copper catalyzed phenylation of indole derivatives by bismuth reagents (Table).

Reaction of triphenylbismuth diacetate 1 and copper diacetate 4 with indole derivatives 12, 15 and 19 led to no phenylated derivatives. When indole 8 was treated with triphenylbismuth bis-trifluoroacetate 2 and copper catalysts 3 or 4 (0.1 eq.), a reaction took place, although no pure products could be isolated in good yield. However, lowering the copper concentration proved beneficial, as a 50% yield of the C(3) phenyl indole 10 was obtained. Even the copper traces present in the solvent[1] were sufficient to induce a 41% yield. When the reaction was performed with C(3) substituted indoles, a different regioselectivity was observed, as only N-phenylation was obtained in moderate yields (15-58%). In the case of carbazole 17, addition of 2 equivalents of 2 in four portions allowed a better yield (84%). C(3) unsubstituted indoles led to the C(3) phenyl derivatives in good yields (60-94%), under mild conditions. Even the 1,2-disubstituted indole 21 was phenylated in good yield. The indole ester 24 followed a different path, as only a moderate yield (30%) of the N-phenyl derivative 25 was obtained. As expected, the 1,3-disubstituted derivative 23 failed to give any phenylation.

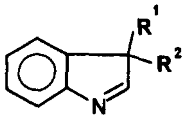
Depending upon the indole substitution pattern, the reaction is believed to follow two different pathways (Scheme). In an initial step the copper catalyst, to which the substrate may already be co-ordinated, reacts with 2 to give a copper (III) species, which reacts to give either a C(3)-Cu 6 or N-Cu 7 intermediate. Reductive elimination then leads to the arylated compounds. As the reaction requires the more reactive bismuth derivative 2, a too high concentration of copper leads to decomposition of the reagent. The synthesis of aryl indoles has been performed by different methods before. Among them, reaction with benzyne gave very low yields of N- and C- phenyl derivatives[12]. Multistep reactions were involved in the case of cationic cyclohexadienyl-iron complex[13]. Phenyl (β-indolyl)iodonium trifluoroacetate, gives the C(3) aryl derivative[14]. Our method is simpler, milder and gives predictable regiochemistry.

We thank Professor J. M. Surzur for generously providing laboratory space.

$Ph_3Bi(OCOR)_2$	$Cu^{\bullet}$	$Cu(OCOR)_2$
1 R=Me	3	4 R=Me
2 R=CF_3		5 R=CF_3

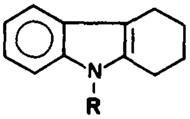


N°	R^1	R^2	R^3
8	H	H	H
9	Ph	H	H
10	H	H	Ph
12	H	H	CH_3
14	Ph	H	CH_3
19	H	CH_3	H
20	H	CH_3	Ph
21	CH_3	CH_3	H
22	CH_3	CH_3	Ph
23	CH_3	H	CH_3
24	H	CO_2Et	H
25	Ph	CO_2Et	H



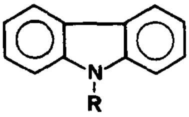
11 $R^1=R^2=Ph$

13 $R^1=CH_3$, $R^2=Ph$



15 R=H

16 R=Ph



17 R=H

18 R=Ph

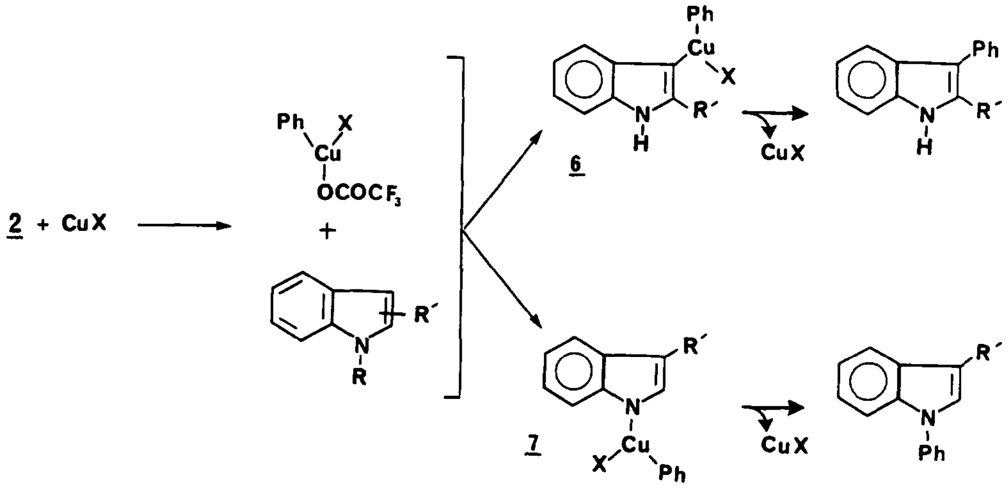
Table - Copper Catalysed Phenylation of Indoles with 2[a]

Indole	2 (eq.)	Catalyst (eq.)	Reaction Time (h)	N-Ph (%)	C(3)-Ph (%)	Other
8	1	3 (0.1)	48	--	--	b
8	1	4 (0.1)	48	--	--	b
8	1.5	3 (0.01)	24	10 (50)		
8	1.5	--	24	10 (41)		
12	1.1	4 (0.1)	20	14 (21)	--	c
15	1	4 (0.1)	5	16 (15)	--	c
17	1	4 (0.1)	24	18 (58)	--	
17	1	5 (0.1)	24	18 (56)	--	
17	4 x 0.5	5 (0.1)	50	18 (84)	--	
19	1	4 (0.1)	24	--	20 (60)	
19	1	3 (0.1)	18	--	20 (96)	
21	1	4 (0.1)	24	--	22 (84)	
21	2.2	4 (0.1)	24	--	22 (87)	
21	1	5 (0.1)	1	--	22 (94)	
24	1	4 (0.1)	24	25 (30)	--	
24	1	3 (0.1)	24	25 (31)	--	

a. All reactions performed in CH_2Cl_2 (10 ml/mmole of substrate) at room temperature until completion (or no evolution) by T.L.C.

b. Complex mixture by T.L.C.

c. Many minor products present, but not isolated from P.T.L.C.



Scheme - Mechanism of the copper catalysed arylation

References

1. D.H.R. Barton, J.P. Finet, and C. Pichon, J. Chem Soc., Chem Comm., 65 (1986).
2. D.H.R. Barton, J.P. Finet, and J. Khamsi, Tetrahedron Letters, 27, 3615 (1986).
3. D.H.R. Barton, J.P. Finet, J. Khamsi and C. Pichon, Tetrahedron Letters, 27, 3619 (1986).
4. D.H.R. Barton, J.P. Finet, and J. Khamsi, Tetrahedron Letters, 28, 887 (1987).
5. G.F. Koser in "The Chemistry of Functional Groups", S. Patai ed., J. Wiley, 1983, Halonium Ions, Chap. 25, p.1286-1310.
6. R.P. Kozyrod and J. T. Pinhey, Aust. J. Chem., 38, 713 (1985).
7. M.E. Kuehne, J. Am. Chem. Soc., 84, 837 (1962).
8. G.L. May and J.T. Pinhey, Aust. J. Chem., 35, 1859 (1982).
9. R.J. Sundberg, "The Chemistry of Indoles", Academic Press, New York 1970; W.J. Houlihan in "The Chemistry of Heterocyclic Compounds", A. Weissberger and E.C. Taylor Eds., Vol. 25, "Indoles", Wiley Interscience.
10. D.H.R. Barton, J.C. Blazejewski, B. Charpiot, J.P. Finet, W.B. Motherwell, M.T.B. Papoula and S.P. Stanforth, J. Chem. Soc., Perkin Trans. 1, 2667 (1985).
11. D.H.R. Barton, J.P. Finet, C. Giannotti, and F. Halley, J. Chem. Soc. Perkin Trans. 1, 241 (1987).
12. M.E. Kuehne and T. Kitagawa, J. Org. Chem., 29, 1270 (1964).
13. L.A.P. Kane-Maguire and C.A. Mansfield, J. Chem. Soc., Chem. Comm., 540 (1973).
14. R.M. Moriarty, Y.Y. Ku, M. Sultana, and A. Tuncay, Tetrahedron Letters, 28, 3071 (1987).

(Received in USA 23 December 1987)