Tetrahedron Letters,Vol.27,No.45,pp 5483-5486,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ACTIVATION OF REDUCING AGENTS. SODIUM HYDRIDE CONTAINING COMPLEX REDUCING AGENTS 23. SYMMETRICAL COUPLING OF NITROGEN-CONTAINING HETEROCYCLIC HALIDES

R. VANDERESSE, M. LOURAK, Y. FORT and P. CAUBERE*

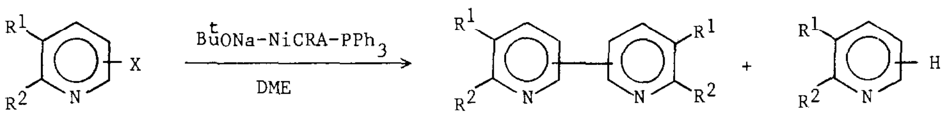
Laboratoire de Chimie Organique I, Associé au CNRS, Université de Nancy I,
BP 239, 54506 VANDOEUVRE-LES-NANCY (FRANCE)

Abstract : The preparation of NiCRA (NaH-$\overset{t}{\text{Bu}}$ONa-Ni(OAc)$_2$) in the presence of PPh$_3$ leads to a reagent (termed NiCRA-PPh$_3$) which is shown to be one of the most efficient Ni containing reagents reported so far for the homocoupling of heteroaromatic halides.

Symmetrical coupling of aryl halides may be performed with either preformed[1] or *in situ* generated[2] transition metal complexes. Whatever their origin, these classical reagents easily couple aryl iodides, less easily aryl bromides or triflates, and scarcely at all aryl chlorides (see for example ref.[3]).

On the contrary, we have already shown[4] that ligand modified NiCRA, i.e. *in situ* prepared mixtures of sodium hydride, sodium alkoxide, nickel acetate and ligand*, very easily couple aryl chlorides as well as bromides. Aryl iodides often lead to large amounts of reduced by-product.

This interesting properties of ligand modified Complex Reducing Agent termed NiCRAL (L = 2,2'-bipyridyl or PPh$_3$) led us to investigate their ability for coupling nitrogen containing aromatic heterocyclic halides. Indeed, coupling such substrates (and particularly the chloro derivatives) is much less easy than coupling simple aryl halides[3b].



---

[*] In the present paper we have adopted the convention given in ref.[5]
Thus a NiCRA-PPh$_3$ prepared from NaH, $\overset{t}{\text{Bu}}$ONa (alkoxide) and nickel acetate in the presence of triphenylphosphine will be abbreviated $\overset{t}{\text{Bu}}$ONa-NiCRA-PPh$_3$ [x:y:z:t] where the molar ratio NaH/RONa/Ni(OAc)$_2$/PPh$_3$ (in that order) is equal to x/y/z/t.

Exploratory experiments showed that NiCRA-PPh_3 was a reagent well suited for the desired reactions. The main side reaction was the reduction which could amount to 50 % yield. A not reported systematic study, showed that the ratio of the components of CRAL, the nature of the solvent as well as the nature of the activating alkoxide all play important roles in these reactions. The best component ratio was determined as being [4:2:1:4] . Among a series of solvents : THF, DME, anisol, hexane-THF, THF-HMPA and anisol-THF, DME was found to be the best and $B\overset{t}{u}ONa$ was determined to be the best activating alkoxide.

With these data in hand we coupled a number of representative heterocyclic halides. The results are gathered in the Table. The results obtained compare very favorably with those of the literature[3a]. It is noteworthy that the yields of coupled products are good, whatever the nature of the halogen and its position relative to that of nitrogen.

Finally the catalytic nature of these reactions was explored with 2-bromo and 2-chloro-6-methoxy pyridines. Using the ratio : $\underline{\text{substrate}}/NaH/B\overset{t}{u}ONa/\underline{Ni(OAc)_2}/PPh_3$ $\underline{4}/4/2/\underline{1}/4$, the yields of coupled products relative to Ni, were found to be 250 % and 285 % respectively.

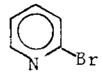
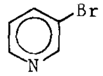
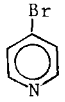
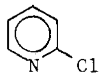
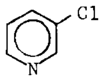
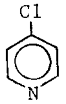
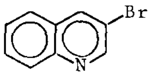
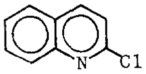
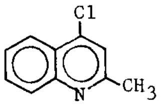
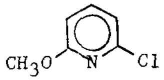
GENERAL PROCEDURE

As previously described[4] the NiCRA-PPh_3 was prepared in DME by addition of $B\overset{t}{u}OH$ to a well stirred mixture of NaH, PPh_3 and nickel acetate at 60°C. After stirring 2 hours at 60°C, the reagent was ready for use. The hetero-aromatic halide and the adequate internal standard in DME (10 ml) were then added to the reagent. The reaction was monitored by GC analysis of small aliquots using a GIRDEL 300 apparatus (flame ionization) equipped with a 2 m 10 % SE 30 column.

After completion of the reaction the excess of NaH was carefully destroyed by dropwise addition of dilute ammonia solution (10 %, 50 ml). The organic phase was extracted with chloroform (3 x 50 ml), dried over magnesium sulfate and evaporated. The residue was chromatographed through a silica gel column using light petroleum (bp 40-70°C)/ether (ratios in parentheses) : 2,2'-, 3,3'-, and 4,4'-bipyridyl (50/50), 6,6'-dimethoxy-2,2'-bipyridyl (98/2), 2,2'-biquinoline (97/3), 3,3'-biquinoline (50/50), 4,4'-biquinaldine(20/80).

3,3'-bipyridyl is very hygroscopic and must be dried by azeotropic distillation with acetone as solvent so that, only traces of water were detectable by Karl Fisher analysis.

TABLE : COUPLING OF HETEROCYCLIC AROMATIC HALIDES.

Substrate (a)	Temperature [°C]	Time [h]	Coupled product % (b)	Reduced product % (b)	mp [°C]	Lit. data
	30	2	65	25 (d)	72	71-73[6]
	45	3	78	20 (d)	67 (e)	68[6]
	45	2	78	20 (d)	113	114[6]
	45	3.5	66	30 (d)	71-72	71-73[6]
	60	5	90	6 (d)	67-68	68[6]
	45	2	86	10 (d)	112-113	114[6]
	45	1.5	72	25	270 (f)	271-271.5[7]
	45	3	68	22	197 (f)	196-198[6]
	45	3.5	71	25	238 (f)(g)	
	45	2.5	79	18	118 (f)	118-119[3b]

(a) The halide/metal molar ratio was always equal to 1

(b) Yields in isolated product, unless otherwise specified

(c) The melting points were determined on a Tottoli apparatus

(d) Determined by GC analysis with internal standard (hydrocarbon C_{12}-C_{14})

(e) Picrate : mp 232°C (lit. 232°C[3b])

(f) The microanalysis of these compounds were in good agreement with the calculated values

(g) ^1H NMR (60 MHz, $CDCl_3$/TMS) : $\delta = 2.78$ (s, 6 H) ; 7.2-7.51 (m, 6 H) ; 7.5-7.92 (m, 2 H) ; 8.11-8.36 (m, 2 H).

REFERENCES

1) See for example : M.F. SEMMELHACK, P. HELQUIST, L.D. JONES, L. KELLER, L. MENDELSON, L. SPELTZ RYONO, J. GORZYNSKI SMITH, and R.D. STAUFFER, J. Am. Chem. Soc. 103, 6460 (1981) and ref. therein.

2) (a) A.S. KENDE, L.S. LIEBESKIND, and D.M. BRAITSCH, Tetrahedron Lett. 1975, 3375 ;
(b) M. ZEMBAYASHI, K. TAMAO, J.I. YOSHIDA, and M. KUMADA, ibid., 1975, 4089.
See also : K. TAKAGI, N. HAYAMA, and S. INOKAWA, Chem. Lett. 1979, 917, and Bull. Chem. Soc. Jpn, 53, 3691 (1980) ; S.I. INABA, H. MATSUMOTO, and R.D. RIEKE, Tetrahedron Lett. 23, 4215 (1982).

3) (a) K. TAKAGI, N. HAYAMA, and K. SASAKI, Bull. Chem. Soc. Jpn, 57, 1887 (1984) ;
(b) M. TIECCO, L. TESTAFFERI, M. TINGOLI, D. CHIANELLI, M. MONTANUCCI, Synthesis 1984, 736.

4) R. VANDERESSE, J.J. BRUNET, and P. CAUBERE, J. Organomet. Chem., 264, 263 (1984).

5) (a) P. CAUBERE, Angew. Chem. Int. Ed. Engl., 22, 599 (1983) ;
(b) P. CAUBERE, Pure and Appl. Chem., 57, 2875 (1985).

6) Handbook of Chemistry and Physics, 63rd Edit., CRC Press, Boca Raton, Florida, 1982.

7) Y. YAMAMOTO and A. YANAGI, Chem. Pharm. Bull., 30, 2003 (1982).

(Received in France 8 September 1986)