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IMPROVED PROCEDURE FOR THE REDUCTIVE PHENYLATION AND CYCLIZATION OF NITROARENES

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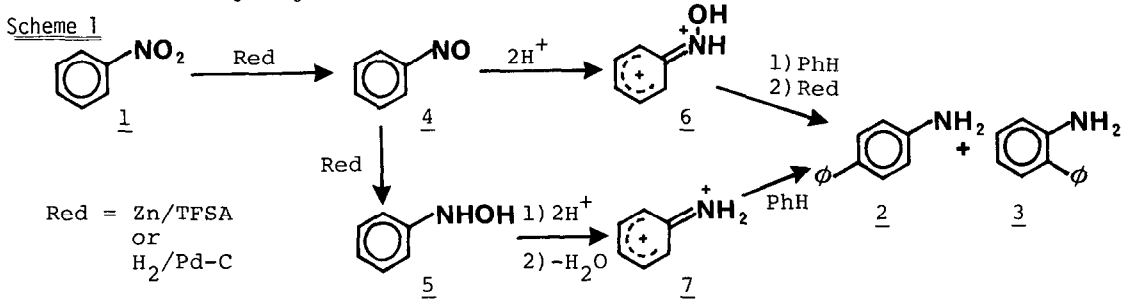
Abstract: The reductive phenylation of nitroarenes was improved by using iron pentacarbonyl (IPC) as a reducing reagent. The method was applied to the synthesis of ellipticine and dibenzazocine derivatives.

Nitrobenzene (1) reacts with benzene in the presence of trifluoromethanesulfonic acid (TFSA) and zinc dust to give 4-aminobiphenyl (2) as a main product (reductive phenylation of nitroarenes).[1] This novel process is a general method for synthesizing aminobiphenyls, and involves iminium-benzenium dications (6 and 7)[2] formed from the intermediates in the reduction process by zinc and acid, i.e., nitrosobenzene (4) and N-phenylhydroxylamine (5) (Scheme 1). Catalytic hydrogenation over Pd/C is also effective for the reductive phenylation.[1] However, these methods are performed in a heterogeneous reaction system, and in some cases this process does not give a good result because of stirring of the reaction mixture and lowering of the acidity of TFSA. We now report a solution to this problem by the use of iron pentacarbonyl (IPC) as the reducing reagent. It is well known that IPC reduces nitroarenes.[3]

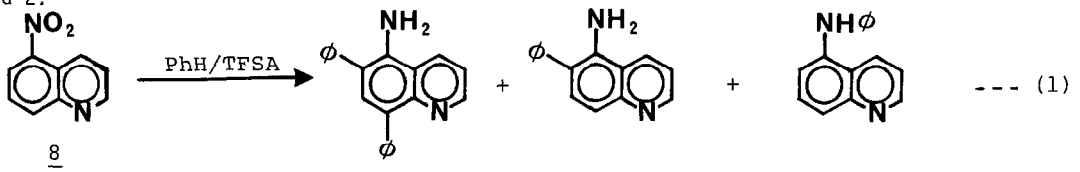
Scheme 1



Direct addition of 1 equivalent of IPC to nitrobenzene (5 mmole) at 5°C in benzene (50 eqt) and TFSA (50 eqt), followed by stirring for 30 min at 5°C and work-up using aqueous sodium hydroxide gave 4-aminobiphenyl (2; 72%) and 2-aminobiphenyl (3; 11%). By the zinc dust method we obtained 2, 3 and aniline in 52, 7 and 30% yields, respectively, adding zinc (6 eqt) in three portions over a period of 3 hr with stirring to an ice-cold mixture of 1 (5 mmole) in benzene (50 eqt) and TFSA (50 eqt). Catalytic hydrogenation of 1 (5 mmole) in benzene (50 eqt)

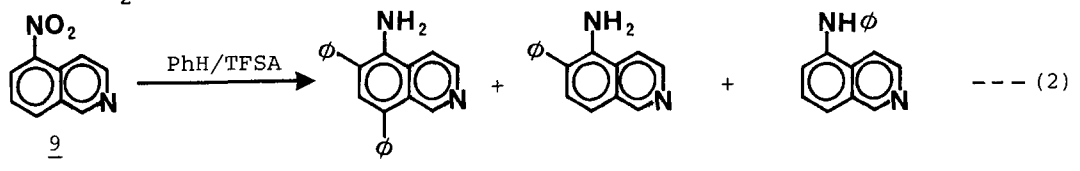
and TFSA (50 eqt) over 10% Pd/C (100 mg) for 5 hr at room temperature gave 2 and 3 in 22 and 5% yields, respectively, accompanied by unreacted 1 (49%). Thus, the IPC method gave the best result among these methods. The advantages of using IPC are the use of one equivalent of reducing reagent and the homogeneity of the medium, resulting in good reproducibity as well as good yields.

5-Nitroquinoline (8) and 5-nitroisoquinoline (9) were also reductively phenylated using the IPC method. Yields of the products and the results by other methods are shown in eqs. 1 and 2.[4]



8 --- (1)

IPC/0°C/30 min	36%	30%	0%
Zn/RT/3 hr	5%	28%	16%
H_2/Pd-C/RT/5 hr	0%	13%	6%

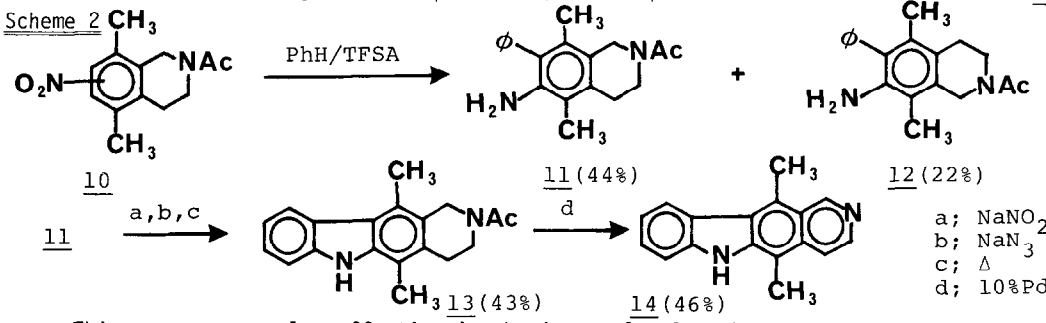


9 --- (2)

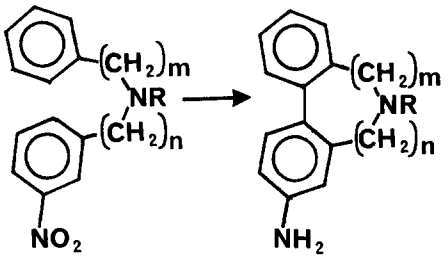
IPC/0°C/30 min	37%	25%	0%
Zn/RT/3 hr	trace	39%	16%
H_2/Pd-C/RT/5 hr	trace	47%	30%

We applied this method to the synthesis of ellipticine.[5] Treatment of an inseparable 1:1 mixture of 2-acetyl-1,2,3,4-tetrahydro-5,8-dimethyl-6- and 7-nitroisoquinoline (10)[6] in benzene (300 eqt) and TFSA (150 eqt) with IPC (3 eqt) at 0°C gave phenyl-aminotetrahydroisoquinolines (11 and 12); this is the key reaction in our synthesis, and it could not be achieved by the zinc and catalytic hydrogenation methods. After separation of these isomers by silica gel chromatography, 11 was converted to ellipticine (14) in 20% overall yield by the procedure shown in the Scheme 2. By the same procedure, isoellipticine[7] was also obtained from 12.

Scheme 2



This process was also effective in the intramolecular phenyl-phenyl coupling reaction of nitroarenes (15) to dibenzo-heterocycles (16), which are of pharmaceutical interest. The results of the IPC reductive cyclization of 15 to 16 are summarized in the Table. Cyclization to an eight-membered dibenzazocine occurred in good yield, when the substituent R on the nitrogen atom of 15 was the Ac, Ts, Ms or CF_3CO group (Table runs 2, 3, 4 and 5). When R was H, the



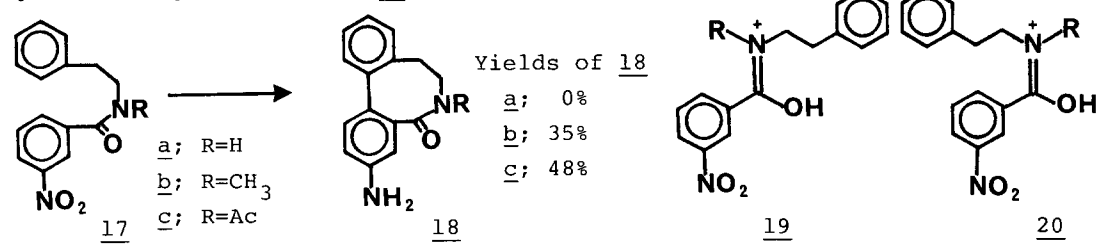
15 16

Table Cyclization of 15 to 16

run	15 m	15 n	15 R	16 ring size	16 yield (%)
1	1	1	Ac	7	72
2	2	1	Ac	8	57
3	2	1	Ts	8	36
4	2	1	Ms	8	66
5	2	1	CF_3CO	8	38
6	2	1	Me	8	26
7	2	1	H	8	8
8	2	2	Ac	9	15
9	2	2	Ts	9	12
10	3	2	Ac	10	30

yield was not satisfactory (run 7). Cyclization to a seven-membered dibenzazepine occurred in good yield (run 1), and cyclizations to a nine-membered dibenzazonine (runs 8 and 9) and to a ten-membered dibenzazenine (run 10) also occurred, but the yields of the products were somewhat low. The major reaction product in these cases was an aniline derivative substituted with a trifluoromethanesulfonyloxy group, which was formed by nucleophilic attack of the trifluoromethanesulfonyloxy anion instead of the intramolecular cyclization of the dication intermediates. A typical procedure was as follows: IPC (2 eqt) was added to a mixture of N-acetyl-(3-nitrobenzyl)-β-phenethylamine (15; m=2, n=1; 2 mmole) and TFSA (100 eqt) with stirring at -30°C. The mixture was stirred for 15 min at -30°C and for 15 min at 0°C then worked up using aqueous potassium carbonate, and separation of the reaction mixture by silica gel chromatography gave colorless needles of 6-acetyl-3-amino-5,6,7,8-tetrahydrodibenz[c,e]azonine in 57% yield (run 2). Using the zinc and catalytic hydrogenation methods, the yields of the azonine were 11 and 42% yields, respectively, in the same cyclization.

Although a secondary amide of type 17a (R=H) did not give a cyclized product, a tertiary amide (17b; R=CH_3)and an imide (17c; R=Ac) gave the expected dibenzazocinones (18) in moderate yields. The dramatic effect of substituents on the amide nitrogen on the yield can probably be accounted for by the assumption that an adverse conformation (19) for the cyclization is predominant when R is H and a favorable one (20) for the cyclization is increased when R is CH_3 or Ac. A similar result was reported in the case of electrochemical cyclization of secondary and tertiary amides such as 17.[8]



a; R=H
b; R=CH_3
c; R=Ac

Yields of 18
a; 0%
b; 35%
c; 48%

17 18 19 20

The reductive cyclization described here has several advantages; the starting nitroarenes can be readily prepared; the reaction conditions are mild enough to keep a functional group such as an amine or amide group intact; activation of the benzene ring or the presence of a special group other than a nitro goup is not required; the work-up procedure is simple. In some cases, the yields are not satisfactory because of competing intermolecular attack of a trifluoromethanesulfonyloxy anion, but this problem may be overcome by activating the benzene ring. Although the number of examples described here is limited, the present method should be very useful for synthesizing aminobiphenyls.[9] We are trying to apply this method to the synthesis of alkaloids.

References and Notes

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(4) Satisfactory elemental analyses and/or spectral result (MASS, IR and NMR) were obtained for all new compounds.

(5) For a review, see: Hewlins, M. J. E.; Oliveira-Campos, A. M.; Shannon, P. V. R. Synthesis 1984, 289.

(6) 10 was prepared by nitration of 1,2,3,4-tetrahydro-5,8-dimethylisoquinoline with potassium nitrate and sulfuric acid followed by N-acetylation with acetic anhydride, which could not be separated by TLC and HPLC.

(7) Isoellipticine: Yellow powder (from ethanol and water); mp >300°C; Mass (m/z) M^+=246; UV (in ethanol) λ_{max}(nm) (logε) 232 (4.324), 274 (4.689), 282 (4.801), 319 (4.778), 332 (4.520); NMR (in DMSO-d_6, δ) 2.96 (3H, s), 3.13 (3H, s), 7.19-7.31 (1H, m), 7.44-7.61 (2H, m), 8.11 (1H, m), 8.34-8.42 (2H, m), 9.55 (1H, bs), 11.35 (1H, s).

(8) Sainsbury, M.; Wyatt, J. J. Chem. Soc. Perkin Trans 1 1977, 1750.

(9) For a review of aryl-aryl bond formation, see: Sainsbury, M. Tetrahedron 1980, 36, 3327.

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