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A mild one-pot deamination of aromatic amines bearing electron-withdrawing groups. Calcium hypophosphite as a dediazonation reagent in nonaqueous media

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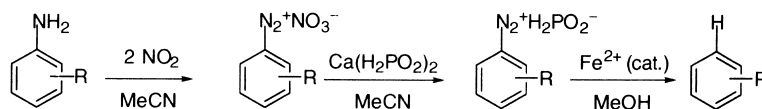
Abstract

Diazotization of the title amines with nitrogen dioxide in acetonitrile at -20°C , followed by treatment with calcium hypophosphite in the presence of methanol and catalytic amounts of iron(II) sulfate at room temperature results in the reductive removal of the amino group, giving the corresponding arenes in moderate to good yield. © 2000 Elsevier Science Ltd. All rights reserved.

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Reductive removal of a nitrogen substituent from organic molecules constitutes an important process in organic synthesis. For primary aromatic amines, they are diazotized and subsequently decomposed in the presence of an appropriate reducing agent. Many reagents have been proposed for this purpose,¹ among which hypophosphorous acid is most preferred in the laboratory.

Hypophosphorous acid is commercially available as 30% aqueous solution. It is produced from calcium hypophosphite $\text{Ca}(\text{H}_2\text{PO}_2)_2$, which in turn is manufactured by boiling white phosphorus in a slurry of lime.² Despite being a cheap precursor to hypophosphorous acid, this salt does not seem to have found use in organic transformation. We wish to report herein that calcium hypophosphite can be used as a mild deamination reagent for less basic aromatic amines under nonaqueous neutral conditions.



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Recently, we have reported the diazotization of aromatic amines with liquid nitrogen dioxide in nonaqueous media.³ This method proved to work especially well with less basic amines bearing electron-withdrawing groups. When calcium hypophosphite was added to the diazotized solution and stirred for a short time at room temperature, nitrogen was evolved and there resulted the parent arenes in good to moderate yield (Table 1; entries 1–6). The reductive deamination was facilitated in the presence of methanol and a transition metal catalyst. The best results were obtained when the reaction was carried out using 4 equiv. of $\text{Ca}(\text{H}_2\text{PO}_2)_2$ and 0.2 equiv. of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ or Cu_2O in a 6:1-mixture of acetonitrile and methanol (Table 2; entries 1 and 3).

Table 1
Deamination of various aromatic amines with $\text{Ca}(\text{H}_2\text{PO}_2)_2^c$

Entry	R	Yield(%) ^b
1	2,4-NO ₂	84
2	2-CN,4-NO ₂	75
3	2-Cl,4-NO ₂	87
4	4-NO ₂	53 (90 ^{c,d})
5	2,4,6-Cl	83 (95 ^d)
6	2-Me,3-NO ₂	41
7	4-Br	16 ^d
8	3,5-Me	15 ^d

^aProducts were identified by direct or spectral comparison with authentic samples. ^bIsolated yield, not optimized. ^cCatalyst 2 mmol. ^dGC yield.

Table 2
Optimization of the reductive deamination of 2,4,6-trichloroaniline^a

Entry	Reagent/mmol ^b	Cosolvent	Catalyst/mmol	Yield(%) ^c
1	$\text{Ca}(\text{H}_2\text{PO}_2)_2/4.0$	MeOH	$\text{Cu}_2\text{O}/0.2$	98
2	$\text{Ca}(\text{H}_2\text{PO}_2)_2/4.0$	MeOH	—	28
3	$\text{Ca}(\text{H}_2\text{PO}_2)_2/4.0$	MeOH	$\text{FeSO}_4/0.2$	95
4	$\text{Ca}(\text{H}_2\text{PO}_2)_2/1.0$	MeOH	$\text{FeSO}_4/0.02$	73
5	$\text{Ca}(\text{H}_2\text{PO}_2)_2/2.0$	MeOH	$\text{FeSO}_4/0.02$	80
6	$\text{Ca}(\text{H}_2\text{PO}_2)_2/4.0$	H ₂ O	$\text{FeSO}_4/0.2$	84
7	$\text{Ca}(\text{H}_2\text{PO}_2)_2/4.0$	— ^d	$\text{FeSO}_4/0.2$	21
8	$\text{H}_3\text{PO}_2/8.0$	— ^e	$\text{FeSO}_4/0.2$	95

^aAll reactions were carried out using substrate (2.0 mmol), NO₂ (0.14 ml, 4.5 mmol), MeCN (30 ml), and a given cosolvent (5 ml). ^b $\text{Ca}(\text{H}_2\text{PO}_2)_2$ was purchased from Wako Pure Chemical Industries, Ltd. ^cGC yield. ^d $\text{Ca}(\text{H}_2\text{PO}_2)_2$ is almost insoluble in MeCN. ^eThe deamination was performed in aqueous acetonitrile.

When the reaction was carried out in the presence of methanol-*O-d*, the product was not deuterated. In the presence of methanol-*d*₄, however, the product was partially deuterated, showing the role of methanol as a competing hydrogen source for aryl radical intermediate.

In summary, calcium hypophosphite can be used as a cheap substitute for hypophosphorous acid in the deamination of aromatic amines. This one-pot deamination method worked well with electron-deficient aromatic amines, but failed with electron-rich ones due to low efficiency of diazotization.

One-pot deamination of aromatic amines in nonaqueous media. Typical procedure: To a stirred solution of 2,4,6-trichloroaniline (0.42 g, 2.1 mmol) in acetonitrile (30 ml) was introduced liquid nitrogen dioxide (0.14 ml, 4.5 mmol) at -20°C (Fume hood). When diazotization was complete, dried $\text{Ca}(\text{H}_2\text{PO}_2)_2$ (0.73 g, 4.3 mmol), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.06 g, 0.2 mmol) and methanol (5 ml) were added successively, and the resulting suspension was stirred for 30 min at room temperature. The mixture was diluted with water (30 ml) and the organic phase was extracted with ether (30 ml \times 3). The combined extracts were washed with brine, dried over Na_2SO_4 , and evaporated to leave a yellow solid, which was purified by chromatography on silica gel using hexane–EtOAc as the eluant to afford 1,3,5-trichlorobenzene (0.32 g, 83%), mp 61–63 $^{\circ}\text{C}$ (lit.⁴ 63.5 $^{\circ}\text{C}$).

References

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