



Zinc-promoted, iridium catalyzed reductive alkylation of primary amines with aliphatic ketones in aqueous medium

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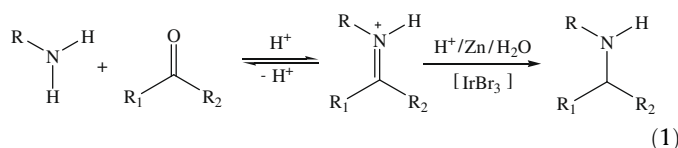
ABSTRACT

The reductive alkylation of primary aromatic and aliphatic amines with aliphatic ketones has been achieved in aqueous acidic medium using commercially available, non-activated zinc dust catalyzed by a very small quantity of iridium bromide. Anilines react well in aqueous formic acid, whereas monoalkylamines require 1,4-dioxane as a co-solvent and sulfuric acid as the proton source. A plausible mechanism via low-valent iridium hydride species is proposed.

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The selective preparation of amines with two or three different substituents is often rather difficult because of the risk of over alkylation, especially in nucleophilic substitution reactions.¹ Direct reductive alkylation via imine or iminium intermediates is the main strategy to avoid this problem and numerous reducing agents have been reported for this transformation. Besides the classical Leuckart–Wallach or Eschweiler–Clarke procedures,² catalytic hydrogenation³ and borane-derived reagents⁴ are most frequently employed. The latter methods often suffer from some restrictions in large-scale preparations due to poor atomic economy because of the loss of some of the active hydride, and from toxicity problems in the case of cyanoborohydrides. Zinc in aqueous acidic medium has also been used occasionally in the past as an inexpensive and environmentally friendly reductant.⁵ A more recent publication describes the reductive alkylation of anilines with aliphatic ketones using activated zinc in acetic acid.^{6a} The same group has reported a similar transformation promoted by magnesium in methanol which was also successful with aliphatic amines.^{6b} However, as both methods need large excess of acid, base, and reactive metals, they do not fulfill the modern requirements of atomic economy and green chemistry.⁷ For the same reason, a related zinc-promoted reduction of preformed imines has also restricted its applicability.⁸

In a recent paper, our group reported a ‘green’ procedure for the selective mono- or dimethylation of amines and amino acids using zinc and aqueous formaldehyde.⁹ Herein, we report the extension of this extremely simple method for the reductive amination of aliphatic ketones (Eq. 1):



Aniline and acetone were chosen for the first explorative experiments using granulated zinc in dilute sulfuric acid, but no alkylation product could be detected at room temperature (Table 1, entry 1). Higher temperature, prolonged reaction time, different acidic additives, or a mixture with organic solvents brought no better results. The decisive influence of transition metal catalysts in several related hydrogenation procedures, especially of Rhodium,¹⁰ Ruthenium,¹¹ and Iridium¹² complexes, prompted a systematic screening for possible catalysts in the zinc-promoted reaction. Indeed, the addition of 2 mg of RhI₃, RuCl₃, Pd(OAc)₂, and PtBr₄ produced trace amounts of *N*-isopropyl aniline (entries 2–5). The best result, a modest 13% yield, was achieved with IrBr₃ (entry 6). Other metal salts (CuI, CuCl₂, NiCl₂, CoCl₂, CdCl₂, and HgCl₂) showed no effect. Once we identified iridium as the most efficient catalyst, the reactivity and nature of the reducing metal were investigated. Replacement of granulated zinc with commercially available, non-activated zinc dust improved the yield to 38% (entry 7). Other metal powders, such as Sn, Mg, Mn, Al, Cr, and In, produced no alkylation product at all. The only exception was iron powder, where the yield was only 10% (entry 8). At this stage, the use of organic solvents was tested again, but only methanol gave a yield comparable to the aqueous reaction; acetonitrile, dimethyl sulfoxide, and 1,4-dioxane gave lower yields (entries 9–12). The concentration of the rather expensive iridium salt was also optimized and it was most gratifying to observe that a decrease from 2 to 0.25 and 0.025 mg of IrBr₃, corresponding to 5.78×10^{-5} mmol, not only maintained, but also increased the yields to 45% (entries 13–15). The reason for this improvement may be explained by the partial solubility of higher amounts of catalyst or by blocking of the active

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Table 1
Optimization of the experimental conditions for reductive alkylation of aniline with acetone^a

Entry	Additive (mmol)	Catalyst (mg)	Metal	Solvent	Time (h)	Yield (%)
1	H ₂ SO ₄ (2)	—	Zn (granules)	H ₂ O	2	—
2	H ₂ SO ₄ (2)	RhI ₃ (2)	Zn (granules)	H ₂ O	2	2
3	H ₂ SO ₄ (2)	RuCl ₃ (2)	Zn (granules)	H ₂ O	2	3
4	H ₂ SO ₄ (2)	Pd(OAc) ₂ (2)	Zn (granules)	H ₂ O	2	1
5	H ₂ SO ₄ (2)	PtBr ₄ (2)	Zn (granules)	H ₂ O	2	1
6	H ₂ SO ₄ (2)	IrBr ₃ (2)	Zn (granules)	H ₂ O	2	13
7	H ₂ SO ₄ (2)	IrBr ₃ (2)	Zn (dust)	H ₂ O	2	38
8	H ₂ SO ₄ (2)	IrBr ₃ (2)	Fe (dust)	H ₂ O	2	10
9	H ₂ SO ₄ (2)	IrBr ₃ (2)	Zn (dust)	MeOH	2	15
10	H ₂ SO ₄ (2)	IrBr ₃ (2)	Zn (dust)	CH ₃ CN	2	—
11	H ₂ SO ₄ (2)	IrBr ₃ (2)	Zn (dust)	DMSO	2	5
12	H ₂ SO ₄ (2)	IrBr ₃ (2)	Zn (dust)	Dioxane	2	16
13	H ₂ SO ₄ (2)	IrBr ₃ (0.25)	Zn (dust)	H ₂ O	2	41
14	H ₂ SO ₄ (2)	IrBr ₃ (0.025)	Zn (dust)	H ₂ O	2	45
15	H ₂ SO ₄ (2)	IrBr ₃ (0.0125)	Zn (dust)	H ₂ O	2	16
16	NaH ₂ PO ₄ (2)	IrBr ₃ (0.025)	Zn (dust)	H ₂ O	4	3
17	HOAc (8)	IrBr ₃ (0.025)	Zn (dust)	H ₂ O	4	55
18	HCOOH (8)	IrBr ₃ (0.025)	Zn (dust)	H ₂ O	4	68
19	HCOOH (8)	IrBr ₃ (0.025) ^c	Zn (dust)	H ₂ O	20	83 (72) ^b

^a General procedure: A mixture of aniline (1 mmol), acetone (3 mmol), additive, catalyst, metal (3 mmol), and the indicated solvent (1 mL) was stirred at 30 °C. After completion of the reaction aqueous ammonia was added and chemical yields were determined by ¹H NMR and GC directly in the CHCl₃- or CCl₄-extract of the free bases in relation to an internal standard.

^b Isolated yield after distillation in a 30 mmol scale.

^c A control experiment in the absence of catalyst gave no product at all.

zinc surface. Although an acidic medium is necessary as a hydroxide source and a catalyst for the iminium ion formation, sulfuric acid appeared to be too strong and cause dissolution of zinc with hydrogen gas evolution. For this reason, less acidic additives were examined. Monobasic sodium phosphate, a very efficient additive in the reductive methylation of amino acids,⁹ was disappointing in the present case (entry 16), but the addition of acetic acid increased the yield to 55% (entry 17). Further progress (68%) was achieved with formic acid and, finally, increasing the reaction time from 4 to 20 h produced a very satisfactory yield of 83% (entries 18

and 19). Under these optimized conditions, several aromatic amines were alkylated with excess acetone in excellent yields (Table 2, entries 1–6). For solubility reasons, the only necessary modification was the use of a twofold quantity of solvent. By changing the carbonyl compound to 2-butanone, results similar to those of acetone were obtained (entries 7–9). When less volatile ketones such as cyclohexanone and cyclopentanone were employed, no excess was necessary to achieve nearly quantitative transformations (entries 10–18), but in some cases a longer reaction time was required. In order to evaluate the diastereoselectivity of our reaction,

Table 2
Reductive alkylation of amines by aliphatic ketones in aqueous acidic medium^a

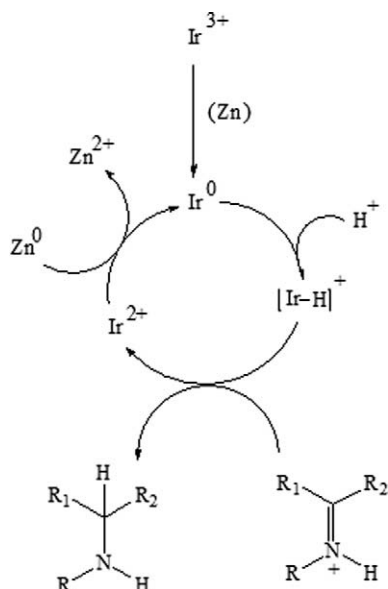
Entry	Amines	Ketones (mmol)	Acid (mmol)	Solvent (mL)	Yield (%)
1	<i>p</i> -CH ₃ -aniline	Acetone (3)	HCO ₂ H (8)	H ₂ O (2)	97
2	<i>p</i> -CH ₃ O-aniline	Acetone (3)	HCO ₂ H (8)	H ₂ O (2)	99 (92) ^c
3	<i>p</i> -Cl-aniline	Acetone (3)	HCO ₂ H (8)	H ₂ O (2)	74
4	<i>p</i> -F-aniline	Acetone (3)	HCO ₂ H (8)	H ₂ O (2)	80
5	α -Naphthylamine	Acetone (3)	HCO ₂ H (8)	H ₂ O (2)	90
6	β -Naphthylamine	Acetone (3)	HCO ₂ H (8)	H ₂ O (2)	99
7	Aniline	Butanone (2)	HCO ₂ H (8)	H ₂ O (2)	100
8 ^b	α -Naphthylamine	Butanone (2)	HCO ₂ H (8)	H ₂ O (2)	98 (92) ^c
9 ^b	β -Naphthylamine	Butanone (2)	HCO ₂ H (8)	H ₂ O (2)	86
10	Aniline	Cyclohexanone (1)	HCO ₂ H (8)	H ₂ O (2)	90
11	<i>p</i> -CH ₃ O-aniline	Cyclohexanone (1)	HCO ₂ H (8)	H ₂ O (2)	100
12	<i>p</i> -Cl-aniline	Cyclohexanone (1)	HCO ₂ H (8)	H ₂ O (2)	80
13	<i>p</i> -F-aniline	Cyclohexanone (1)	HCO ₂ H (8)	H ₂ O (2)	100
14	α -Naphthylamine	Cyclohexanone (1)	HCO ₂ H (8)	H ₂ O (2)	87 (82) ^c
15	β -Naphthylamine	Cyclohexanone (1)	HCO ₂ H (8)	H ₂ O (2)	69 (63) ^c
16	Aniline	Cyclopentanone (1)	HCO ₂ H (8)	H ₂ O (2)	85
17 ^b	α -Naphthylamine	Cyclopentanone (1)	HCO ₂ H (8)	H ₂ O (2)	90 (86) ^c
18 ^b	β -Naphthylamine	Cyclopentanone (1)	HCO ₂ H (8)	H ₂ O (2)	75 (70) ^c
19	Aniline	2-Methylcyclohexanone (1)	HCO ₂ H (8)	H ₂ O (2)	75 (85:15) ^d
20	Aniline	3-Methylcyclohexanone (1)	HCO ₂ H (8)	H ₂ O (2)	80 (35:65) ^d
21 ^b	Benzylamine	Acetone (3)	H ₂ SO ₄ (1.4)	Dioxane/H ₂ O (1/0.25)	88
22 ^b	Benzylamine	Butanone (2)	H ₂ SO ₄ (1.4)	Dioxane/H ₂ O (1/0.25)	99
23 ^b	Benzylamine	Cyclopentanone (1)	H ₂ SO ₄ (1.4)	Dioxane/H ₂ O (1/0.25)	70
24 ^b	CH ₃ NH ₂ ·HCl (5)	Cyclopentanone (1)	—	Dioxane/H ₂ O (1/0.025)	78
25 ^b	CH ₃ NH ₂ ·HCl (5)	Cyclohexanone (1)	—	Dioxane/H ₂ O (1/0.025)	85 (84) ^c

^a Amine (1 mmol), ketone, IrBr₃ (0.025 mg), zinc (3 mmol), 20 h.

^b Reaction time: 72 h.

^c Isolated as picrate.

^d *syn/anti* ratio.



Scheme 1. Possible mechanism of reductive alkylation catalyzed by Ir.

2- and 3-methylcyclohexanone were allowed to react with aniline. In the first case, an interesting *syn/anti* ratio of 85:15 was observed (entry 19), a result comparable to those obtained earlier with sterically hindered borane reagents.¹³ For 3-methylcyclohexanone, a weak anti-selectivity was observed, also in good agreement with the results reported for borohydride reduction (entry 20).¹⁴

Initial attempts to extend the procedure to aliphatic primary amines failed in aqueous solution. However, a systematic search for alternative conditions led to 1,4-dioxane/water 4:1 as the best solvent, 1.4 mmol of sulfuric acid as additive, and the same low catalyst concentration as before. Under these modified reaction conditions benzylamine and methylamine hydrochloride could be alkylated with acyclic and cyclic ketones in preparative yields (entries 21–25).

Two mechanisms can be proposed in the present reaction: reduction by an iridium hydride intermediate and catalytic hydrogenation on the surface of metallic iridium. The latter possibility was excluded by a control experiment in a hydrogen atmosphere under the conditions shown in entry 19 (Table 1), but in the absence of metallic zinc, no trace of reductive amination was detected. Consequently, a low-valent iridium hydride species produced by Zn-reduction in acidic medium can be envisaged (Scheme 1). After the transfer of the hydride to iminium ion, Ir²⁺ is recycled to Ir⁰ by Zn-reduction and generates a new iridium hy-

dride species to continue the reaction. This cyclic catalytic process is analogous to the related reductive amination of aldehydes catalyzed by Ir-complexes in aqueous acid¹⁵ and organic medium¹⁶ where triethyl silane was used as the hydride donor. Also, a recently described reductive amination by Ir-catalyzed hydrogenation in organic solvents or ionic liquids at high temperature may proceed by a similar mechanism.¹⁷

In comparison with the last three procedures, the reductive amination described in the present work is characterized by an extremely simple and safe experimental procedure with no side products. The method employs aqueous solvent, open atmosphere, room temperature, inexpensive reagents, and simple Ir-salts as catalysts in a very low concentration (5×10^{-5} mmol). All these features fulfill the basic principles of green chemistry.

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