Cerium(IV)-Promoted Ethylation of Schiff Bases by Triethylaluminum

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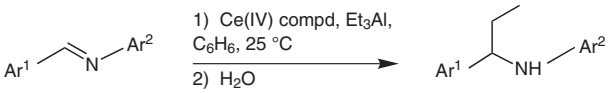
Abstract: Schiff bases $Ar^1CH=NAr^2$ that are refractory towards Et_3Al are activated at room temperature by cerium(IV) compounds. The ethylation takes place selectively at the methine moiety of the imine. The process is strongly influenced by steric hindrance and depends on the electronic nature of the substrate: electron-donating substituents promote the reaction while electron-withdrawing groups cause it to slow down. Application of cerium(IV) ammonium nitrate as promoter gives the best results. In the absence of excess Et_3Al it causes, however, transformation of the Schiff base to the corresponding aldehydes and amines.

Key words: cerium(IV) compounds, C-ethylation, lanthanides, Schiff bases, triethylaluminum

Although triethylaluminum is a powerful ethylation reagent for many carbon–carbon and carbon–heteroatom double bonds,[1] it fails to affect Schiff bases under standard laboratory conditions.[2] Recently, however, the group of Szymoniak and our own group have succeeded in activating Et_3Al for the ethylation of Schiff bases by applying either dicyclopentadienylzirconium(IV)[3], or some europium(III) or praseodymium(III) shift reagents as catalysts.[4] We have now attempted to extend this study and use, in the reaction of PhCH=NPh and Et_3Al, a series of chlorides of other trivalent rare earths elements. Unfortunately, only low yields of ethylation could be achieved. Furthermore, the neodymium and thulium salts led to contamination of the expected product with the non-alkylated amine, and the yttrium chloride afforded solely this ethyl-deficient amine (see Table 1). Curiously $CeCl_3$, which has already been shown to have a stimulating effect on the cross-coupling reactions of Et_3Al,[5] proved completely inactive in the Schiff base ethylation. However, by replacing $CeCl_3$ by cerium(IV) compounds, alkylation of a variety of imines could be accomplished at room or even at sub-room temperature. Representative results of this regioselective ethylation are shown in Scheme 1 and summarized in Table 2.



Scheme 1

Table 1 Ethylation of PhCH=NPh by Et_3Al in the Presence of Lanthanide Trichlorides under Comparable Conditions[a]

Entry	Rare earth compound	Yield of products (%)[b]	
		PhCH(Et)NHPh	$PhCH_2NHPh$
1	$LaCl_3$	9	0
2	$NdCl_3$	25	10
3	$SmCl_3$	19	0
4	$TmCl_3$	20	15
5	$LuCl_3$	8	0
6	YCl_3	0	11

[a] Reaction conditions: Schiff base (3.35 mmol) in benzophenone ketyl dried benzene (30 mL). $LnCl_3$ (3.35 mmol) and Et_3Al (1M, in hexane, 3.35 mmol); r.t. , 24 h under Ar.

[b] Yields of the isolated products are the average of at least two experiments that did not differ by more than ±2%. The missing percentage reflects the unreacted Schiff base.

Table 2 indicates that among the three Ce(IV) derivatives studied, cerium ammonium hexanitrate (CAN), cerium sulfate and cerium tetrafluoride, the former is by far the most effective promoter. In the presence of excess Et_3Al (three equivalents) electron-neutral and electron-rich imines form almost quantitative yields of the ethylation product (see entries 3, 4, 12 and 14). Although CAN acts as a catalyst, we usually employed 0.75–1 equivalent relative to the substrate in order to achieve good yields within a reasonable time. At lower CAN:substrate ratios (see e.g., entry 6), the alkylation could be brought to completion only after considerable extension of the reaction period. The application of three equivalents of Et_3Al is necessary in order to prevent substantial transformation of the Schiff bases back to aldehydes during the ethylation (vide infra). Under these conditions, relatively small amounts of the corresponding aldehydes were formed in only three of the cases studied (entries 13, 15 and 19). Neither $Ce(SO_4)_2$ nor CeF_4 causes the formation of PhCHO during the ethylation process.

Table 2 reveals also that the CAN-promoted ethylation depends on the electronic nature of the substrate. While the unsubstituted imine (entry 3), and the one substituted by a methyl group at the benzylidene moiety (entry 10) react quite fast, the Cl, Br and CN substituted imines (entries 13,15 and 16) are ethylated at a slower rate. This

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Table 2 Ethylation of Schiff Bases $Ar^1CH=NAr^2$ by Et_3Al in the Presence of Cerium(IV) Compounds[a]

Entry	Substrate		Et_3Al (equiv)	Cerium compd (equiv)[b]	Products, yield (%)[c]
	Ar^1	Ar^2			
1	Ph	Ph	1.0	CAN (1.0)	PhCH(Et)NHPh (37), PhCHO (45)[d]
2	Ph	Ph	1.0	CAN (0.5)	PhCH(Et)NHPh (35), PhCHO (34)[d]
3	Ph	Ph	3.0	CAN (1.0)	PhCH(Et)NHPh (93)
4	Ph	Ph	3.0	CAN (0.75)	PhCH(Et)NHPh (93)
5	Ph	Ph	3.0	CAN (0.25)	PhCH(Et)NHPh (77)
6	Ph	Ph	3.0	CAN (0.1)	PhCH(Et)NHPh (49)
7	Ph	Ph	1.0[e]	$Ce(SO_4)_2$ (1.0)	PhCH(Et)NHPh (13)
8	Ph	Ph	1.0	CeF_4 (1.0)	PhCH(Et)NHPh (32)
9	Ph	Ph	2.0[e]	CeF_4 (1.0)	PhCH(Et)NHPh (64)
10	4-MeC_6H_4	Ph	3.0	CAN (0.75)	4-MeC_6H_4CH(Et)NHPh (85)
11	4-MeC_6H_4	Ph	3.0	CeF_4 (0.75)	4-MeC_6H_4CH(Et)NHPh (26), 4-$MeC_6H_4CH_2$NHPh (22)
12	Ph	4-$MeOC_6H_4$	3.0	CAN (0.75)	PhCH(Et)NHC_6H_4-4-OMe (99)
13	4-ClC_6H_4	Ph	3.0[f]	CAN (0.75)	4-ClC_6H_4CH(Et)NHPh (57), 4-ClC_6H_4CHO (19)[d]
14	Ph	4-ClC_6H_4	3.0	CAN (0.75)	PhCH(Et)NHC_6H_4-4-Cl (98),
15	4-BrC_6H_4	Ph	3.0	CAN (0.75)	4-BrC_6H_4(Et)NHPh (28), 4-BrC_6H_4CHO (11)[d] 4-$BrCH_2$NHPh (26)
16	4-NCC_6H_4	Ph	3.0	CAN (0.75)	4-NCC_6H_4CH(Et)NHPh (50)
17	3-HOC_6H_4	Ph	3.0[g]	CAN (0.75)	3-HOC_6H_4CH(Et)NHPh (98)
18	2-C_5H_4N	Ph	3.0	CAN (0.75)	2-C_5H_4NCH(Et)NHPh (99)
19	Ph	2-$C_{10}H_7$	3.0	CAN (0.75)	PhCH(Et)NH-2-$C_{10}H_7$ (58), PhCHO (8)[d]

[a] Reaction conditions: Schiff base (3.35 mmol) in benzophenone ketyl-dried benzene (30 mL). Treatment with the calculated amount of the cerium compound and Et_3Al (1 M) at 25 °C, 20 h under Ar.
[b] CAN = ceriumammonium hexanitrate.
[c] The results are the average of at least two experiments that did not differ by more than ±3%. The missing percentage reflects the unreacted Schiff base.
[d] Contaminated with varying amounts of aniline (or its derivatives) which could not be determined quantitatively.
[e] No change in yield was observed when the number of equivalents was increased to 3.0.
[f] When the number of equivalents was reduced to 1.0 the yield of the aldehyde increased to 41%.
[g] In the absence of excess (>1.0 equivalents) Et_3Al, no alkylation took place.

electronic effect is opposite to that observed in the lanthanide(III)-catalyzed ethylation of Schiff bases by Et_3Al where electron-withdrawing groups increase the rate and electron-donating functions slow it down. The substituents on the aniline moiety do not seem to have a significant effect on the rate (cf., entries 12 and 14). The low yield of the ethylation of *N*-(4-bromophenyl)methylene-*N*-phenylamine (entry 15) may be associated with the formation of free radicals by the aromatic bromine atom.[6] Curiously, when an equimolar mixture of 4-$BrC_6H_4CH=NC_6H_5$ and 4-$NCC_6H_4CH=NC_6H_5$ were reacted with Et_3Al and CAN, only the bromo compound reacted and the cyano-substituted Schiff base remained unaffected. The ethylation of *N*-(3-hydroxyphenyl)methylene-*N*-phenylamine (entry 17) is remarkable. Although the hydroxyl group destroys one equivalent of the aluminum reagent (and therefore equimolar quantities of the substrate and the ethylating reagent do not yield the expected product) the use of excess Et_3Al permits smooth ethylation of the Schiff base.

Steric hindrance, too, has an effect on the ethylation. Thus, while *N*-2-naphthyl-*N*-(phenylmethylen)amine is ethylated as indicated in entry 19, the more hindered 1-naphthyl isomer does not react with Et_3Al in the presence of CAN. Likewise, substitution of the phenyl group of the parent Schiff base with methylated equivalents such as *N*-

(2,6-dimethylphenyl)methylene-*N*-phenylamine, prevents the ethylation. We have noticed previously[4] that the Schiff base formed from aniline and 2-pyridinecarboxaldehyde reacts slowly with Et_3Al even in the absence of a catalyst. The reaction rate is however, increased in the presence of CAN. We rationalized this phenomenon by the possible formation of a reactive aluminum–imine complex via the pyridine nitrogen atom (cf., such complexes with Me_3Al and Me_3Ga, reported in reference 7). The tendency of the aluminum reagent to form complexes with heteroatoms[1] led us to choose hetereoatom-free solvents for our process. Reactions in aromatic hydrocarbons (benzene, toluene) and in aliphatic ones (*n*-hexane) have been found to proceed equally well provided the substrates are soluble in these solvents. No ethylation takes place in THF. Studies at a wide range of reaction temperatures, from –78 to 80 °C, revealed that the best results, where minimum side products were formed, were obtained between 20 and 30 °C.

The ethylations listed in Tables 1 and 2 require the complete absence of moisture, otherwise the Schiff bases undergo catalytic hydrolysis into the starting aldehydes and amines. While the aldehydes can be isolated, the interaction of the amines with the aluminum reagents usually prevents their complete isolation from the reaction mixtures. For this reason,, the hygroscopic lanthanide salts were dried over P_2O_5, in the dark, under reduced pressure for at least one week prior to their application. Nevertheless, the formation of the aldehyde was still found to take place (in the absence of excess Et_3Al) whenever CAN was employed, even in its purest anhydrous state. No hydrolysis was observed when other lanthanide derivatives, including the Ce(IV) compounds $Ce(SO_4)_2$ and CeF_4 were used. Since both the reactions of CAN[8] and some other additions to C=N double bonds of imines were shown to occasionally involve free radicals,[9] we performed the ethylation listed as entries 1–3 in Table 1 in the presence of either benzoyl peroxide or AIBN. As neither free radical initiators caused any changes in the rate of ethylation nor altered the ratio between PhCH(Et)NHPh and PhCHO, we conclude that the formation of the ethylated amine and of the aldehyde (in the presence of stoichiometric quantities of Et_3Al) do not involve a free radical mechanism. Because the benzaldehydes are formed only in the presence of CAN and neither with $Ce(SO_4)_2$ nor with CeF_4, we assume that the amount of water required for the hydrolysis process originates from the $(NH_4)_2Ce(NO_3)_6$, via a redox reaction between the nitrate anions, NO_3^- of CAN and aluminum hydride species Et_nAlH_{3-n}, formed by β-hydride elimination of $CH_2=CH_2$ from $AlEt_3$.[1] Support for this assumption was found in an experiment in which the reaction mixture described in entry 1 of Table 2 gave, upon treatment with aqueous $FeSO_4$, a positive indication for the presence of nitrite as the reduction product of NO_3^-.

The ability of CAN to promote the ethylation of Schiff bases while Ce(III) derivatives are completely inactive and $Ce(SO_4)_2$, CeF_4, and other Ln(III) compounds are less active, may also be rationalized by this redox process provoking the activation of the triethylaluminum.

In conclusion, some Ce(IV) compounds, used frequently as oxidizing reagents, promote room temperature selective C-ethylation of sterically unhindered Schiff bases by Et_3Al. Cerium(IV) ammonium nitrate acts as a catalyst and is more active than cerium(IV) sulfate and cerium(IV) fluoride. However, in the absence of excess Et_3Al, CAN also promotes the hydrolysis of unreacted Schiff base to the corresponding starting components, presumably by a redox process that involves the nitro groups of CAN and the disproportionated ethylation reagent.

The various Schiff bases were prepared mostly from commercially available aldehydes and amines (Aldrich Chemical Co.) by the conventional methods summarized by Vázquez et al.[11] and the properties of PhCH=NPh,[4] 4-MeC_6H_4CH=NPh,[4] 2,6-$Me_2C_6H_3$CH=NPh,[12] PhCH=NC_6H_4-4-OMe,[13] 4-ClC_6H_4CH=NHPh,[4] PhCH=NC_6H_4-4-Cl,[13] 4-BrC_6H_4CH=NPh,[12] 4-NCC_6H_4CH = NPh,[4] 3-HOC_6H_4CH=NPh,[14] PhCH=N-1-$C_{10}H_7$,[15] PhCH=N-2-$C_{10}H_7$,[16] and (2-C_5H_4N)CH=NPh[4] were comparable to those reported previously. The reference compounds for the ethylated Schiff bases PhCH(Et)NHPh,[4] 4-MeC_6H_4CH(Et)NHPh,[4] PhCH(Et)NHC_6H_4-4-OCH_3,[3] PhCH(Et)NHC_6H_4-4-Cl,[13] 4-NCC_6H_4CH(Et)NHPh[4] and 2-(C_5H_4N)CH(Et)NHPh[4] were prepared as described in the literature. The non-ethylated amines were obtained by Pd–C-catalyzed hydrogenation of the corresponding Schiff bases. The lanthanide compounds were obtained from Aldrich Chemical Co. and from Alfa Aesar in the purest state available.

Infrared spectra were taken on a Bruker Vector 22-FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-300 instrument. Mass spectral measurements were performed on a Hewlett-Packard model 4989A mass spectrometer equipped with an HP gas chromatograph model 5890 series II. Gas chromatographic separations and analysis were carried out with the aid of a computer-operated Hewlett-Packard model Agilent 4890D gas chromatograph.

Cerium(IV)-Promoted Ethylation of Schiff Bases; General Procedure

The Schiff base (3.35 mmol) was dissolved under exclusion of air at r.t. (25 °C) in benzophenone ketyl dried benzene (30 mL). The mixture was stirred for 10 min and the appropriate cerium(IV) compound (2.53 mmol) was added. After 20 min, Et_3Al (1 M in *n*-hexane, 10.05 mL, 10.05 mmol) was added to the suspension. The mixture was stirred at r.t. for 20 h and then quenched either with H_2O alone (100 mL) or with MeOH (80 mL) and KOH (15 g). The mixture was extracted with Et_2O (2 × 100 mL). The organic layer was then washed with H_2O (2 × 100 mL), dried over $MgSO_4$ and concentrated. The crude products were then purified either by column chromatography or by distillation under reduced pressure. The purity of the known products were determined by gas chromatography and their ^1H and ^{13}C NMR, IR and MS compared with those of authentic samples.

***N*-[1-(4-Bromophenyl)propyl]phenylamine**

Yellow-brown viscous oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.82 (dq, $J_d = J_q$ = 7.5 Hz, 2 H, CH_2), 4.22 (t, *J* = 7.5 Hz, 1 H, CH), 6.48 (d, *J* = 8 Hz, 2 H, ArH), 6.70 (t, *J* = 8 Hz, 1 H, ArH), 7.10 (t, *J* = 8 Hz, 2 H, ArH), 7.25 (t, *J* = 8 Hz, 2 H, ArH), 7.43 (d, *J* = 8 Hz, 2 H, CBrCH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.9, 31.7, 59.3, 113.4, 117.5, 120.6, 126.6, 128.4, 129.2, 143.2, 147.3.

MS (EI, 70 eV): *m/z* (%) = 287, 289 (16) $[M - 2H]^+$, 260, 258 (100) $[C_{13}H_9BrN]^+$, 179 (15) $[C_{13}H_9N]^+$, 170, 168 (18) $[C_7H_5Br]^+$, 117 (13) $[C_9H_9]^+$, 115 (14) $[C_9H_7]^+$, 104 (93) $[C_7H_6N]^+$, 93 (19) $[C_6H_7N]^+$, 91 (17) $[C_6H_5N]^+$, 77 (54) $[C_6H_5]^+$.

Anal. Calcd for $C_{15}H_{16}BrN$: C, 62.08; H, 5.56; N, 4.83. Found: C, 62.49; H, 5.95; N, 4.76.

_N_-[1-(3-Hydroxyphenyl)propyl)]phenylamine
Pale-yellow viscous oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.5 Hz, 3 H, CH_3), 1.97 (dq, $J_d = J_q$ = 7.5 Hz, 2 H), 3.95 (br s, NH, 1 H), 4.19 (t, J = 7.5 Hz, CH, 1 H), 4.42 (s, 1 H, OH), 6.78 (t, J = 8 Hz, 3 H, ArH), 6.88–7.15 (m, ArH, 5 H), 7.17 (t, J = 8 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7, 29.6, 62.9, 115.2, 116.0, 117.1, 120.1, 121.1, 126.1, 128.4, 128.5, 129.3, 129.4, 146.8, 156.5.

MS (EI, 70 eV): *m/z* (%) = 209 (100) $[M\text{-}H_2O]^+$, 180 (89) $[C_{13}H_{10}N]^+$, 151 (42) $[C_9H_{11}NO]^+$, 104 (27) $[C_7H_6N]^+$, 93 (46) $[C_6H_7N]^+$, 76 (45) $[C_6H_4]^+$.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.18; H, 7.51; N, 6.14.

_N_-(2-Naphthyl)-_N_-(1-phenylpropyl)amine
Yellow viscous oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.5 Hz, 3 H, CH_3), 1.93 (dq, $J_d = J_q$ = 7.5 Hz, 2 H, CH_2), 4.00 (br s, 1 H, NH), 4.37 (t, J = 7.5 Hz, 1 H, CH), 6.67 (s, 1 H, ArH), 6.90 (d, J = 8 Hz, 1 H, ArH), 7.15 (t, J = 7.5 Hz, 1 H, ArH), 7.23 (t, J = 7.5 Hz, 1 H, ArH), 7.29–7.41 (m, 5 H, ArH), 7.46 (d, J = 8 Hz, 1 H, ArH), 7.57 (d, J = 8 Hz, 1 H, ArH), 7.61 (d, J = 8 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0, 31.6, 59.8, 105.6, 118.2, 122.0, 126.1, 126.3, 126.6, 127.1, 127.5, 127.7, 128.7, 128.9, 143.71, 145.16.

MS (EI, 70 eV): *m/z* (%) = 259 (34) $[M - 2H]^+$, 230 (100) $[C_{17}H_{12}N]^+$, 153 (5) $[C_{11}H_7N]^+$, 142 (11) $[C_{10}H_8N]^+$, 126 (19) $[C_{10}H_6]^+$, 114 (15) $[C_9H_6]^+$, 91 (27) $[C_7H_7]^+$, 77 (9) $[C_6H_5]^+$.

Anal. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.40; H, 7.38; N, 5.36.

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