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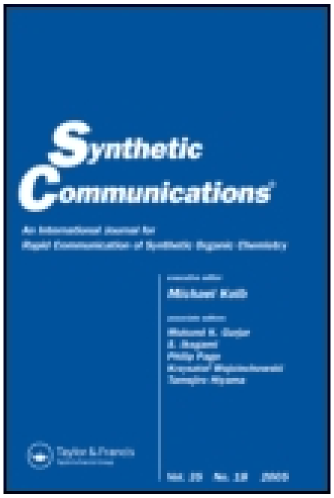

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La(O-i-Pr)$_3$ CATALYZED THREE-COMPONENT CONDENSATION REACTION: A CONVENIENT SYNTHESIS OF N,N-DIALKYL-α-CYANOAMINES

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La(O-i-Pr)$_3$ CATALYZED THREE-COMPONENT CONDENSATION REACTION: A CONVENIENT SYNTHESIS OF *N*,*N*-DIALKYL-α-CYANOAMINES

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ABSTRACT

In the presence of 10 mol% of La(O-i-Pr)$_3$, a three-component condensation reaction of aldehyde, secondary amine and trimethylsilylcyanide proceeded smoothly to afford *N*,*N*-dialkyl-α-cyanoamine in good yield.

Key Words: La(O-i-Pr)$_3$; Three-component condensation; One-pot synthesis; *N*,*N*-dialkyl-α-cyanoamine

During recent years, the use of lanthanide(III) compounds as catalysts or promoters in organic synthesis have attracted great interest.[1] Very recently, we have reported a series of organic reactions catalyzed

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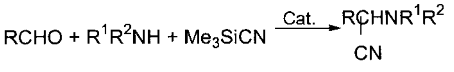
by rare earth metals, such as ene reaction,[2a] one-pot synthesis of amino phosphonates,[2b] imino Diels–Alder reaction,[2c] [2 + 2] cycloaddition reaction,[2d] Biginelli reaction[2e] as well as the addition of silyl ketene acetals to nitrones.[2f]

Bifunctional α-amino nitriles are versatile intermediates in organic synthesis. It also exhibit a valuable dual reactivity, which has been utilized in a broad range of synthetic applications.[3] One of the important methods for the synthesis of amine derivatives is a three-component condensation in the presence of Lewis acid.[4] However, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. In other cases, more than stoichiometric amounts of the Lewis acids are needed because the acids are trapped by nitrogen.[4b,5] The reaction of organometallic nucleophiles with imines or acylimines prepared from aldehydes and primary amines or carbamates is an useful method for the preparation of bifunctional amine derivatives. But it is not suitable for the synthesis of *N*,*N*-disubstituted amine derivatives. Herein, we wish to report a convenient synthesis of *N*,*N*-dialkyl-α-cyanoamines from one-pot condensation of aldehydes, secondary amines and trimethylsilylcyanide using La(*O*-i-Pr)$_3$ as catalyst (Sch. 1).

At first, several kinds of Lewis acids were examined in the model reaction (R=Ph, $R^1=R^2=CH_2Ph$), and the results are summarized in Table 1.

Traditional Lewis acids, such as $ZnCl_2$ and $SnCl_2$ cannot catalyze this three-component condensation reaction at all. Among all the lanthanide catalysts screened, La(*O*-i-Pr)$_3$ showed the better catalytic activity. In the presence of 10 mol% of La(*O*-i-Pr)$_3$, the condensation reaction of benzaldehyde, dibenzylamine and trimethylsilylcyanide proceeded smoothly to afford *N*,*N*-dibenzyl-α-cyanoamine with 78% yield in 10 h at 40°C. Increasing the catalyst amount did not show an evidently better effect. On the other hand, the lower reaction temperature (<20°C) would lead to the decrease of the yield. THF was found to be a superior solvent than any others.

Several other aldehydes and secondary amines were examined under the optimal reaction conditions: (10 mol% La(*O*-i-Pr)$_3$ at 40°C in THF).[6] The result are listed in Table 2. To most of the substrates we used, the reaction can be completed in 8–15 h and give the products in good yields. The electron-donating and electron-withdrawing groups on the benzene ring of aromatic aldehydes did not affect the yields of the products. But the reaction of aliphatic aldehyde was rather difficult. For the α,β-unsaturated



$$RCHO + R^1R^2NH + Me_3SiCN \xrightarrow{Cat.} \underset{\displaystyle CN}{RCH}NR^1R^2$$

1-14

Scheme 1.

Table 1. Optimal Reaction Conditions of the Three-Component Condensation Reaction ($R{=}Ph$, $R^1{=}R^2{=}CH_2Ph$)

Entry	Catalyst	Temp. (°C)	Time (h)	Solv.	Yield[a] (%)
1	$La(O\text{-}i\text{-}Pr)_3$	20	14	THF	67
2	$La(O\text{-}i\text{-}Pr)_3$	40	10	THF	78 (62[b],79[c])
3	$La(O\text{-}i\text{-}Pr)_3$	60	10	THF	77
4	$La(O\text{-}i\text{-}Pr)_3$	40	10	Toluene	64
5	$La(O\text{-}i\text{-}Pr)_3$	40	12	CH_2Cl_2	51
6	$La(O\text{-}i\text{-}Pr)_3$	Refluxing	12	Et_2O	71
7	$Sm(O\text{-}i\text{-}Pr)_3$	40	10	THF	72
8	$Yb(O\text{-}i\text{-}Pr)_3$	40	10	THF	70
9	$La(OTf)_3$	40	10	THF	72
10	$LaCl_3$	40	12	THF	28
11	$ZnCl_2$	40	15	THF	0
12	$SnCl_2$	40	15	THF	0

[a] Isolated yields. [b] 5 mol% catalyst. [c] 20 mol% catalyst.

Table 2. The Results of the Condensation Reaction Catalyzed by $La(O\text{-}i\text{-}Pr)_3$[a]

Entry	R	R^1	R^2	Time (h)	Yield[b] (%)
1	Ph	$PhCH_2$	$PhCH_2$	10	78
2	PhCH=CH	$PhCH_2$	$PhCH_2$	10	81
3	*p*-$CH_3OC_6H_4$	$PhCH_2$	$PhCH_2$	15	72
4	*p*-$O_2NC_6H_4$	$PhCH_2$	$PhCH_2$	8	75
5	*p*-BrC_6H_4	$PhCH_2$	$PhCH_2$	8	82
6	2-pyridin	$PhCH_2$	$PhCH_2$	8	65
7	2,4-di-Cl-C_6H_3	$PhCH_2$	$PhCH_2$	8	80
8	Ph	$(CH_3)_2CH$	$(CH_3)_2CH$	15	45
9	Ph	$CH_2CH_2CH_2CH_2CH_2$		12	78
10	PhCH=CH	$CH_2CH_2CH_2CH_2CH_2$		10	72
11	*p*-BrC_6H_4	$CH_2CH_2CH_2CH_2CH_2$		10	64
12	$(CH_3)_2CH$	$PhCH_2$	$PhCH_2$	15	trace
13	Ph	$PhCH_2$	CH_3	10	71
14	*p*-BrC_4H_6	$PhCH_2$	CH_3	10	76

[a] 10 mol% cat., 40°C, THF. [b] Isolated yields.

aldehyde, the reaction took place perfectly in 1,2-position, and the carbon–carbon double bond was not affected (Entries 2 and 10, Table 2).

In summary, we have found a novel and convenient method for the synthesis of *N*,*N*-dialkyl substituted α-cyanoamines by a Lewis acid catalyzed three-component condensation reaction. It has some noteworthy features, such as good yields and operational simplicity. It also enlarged the application sale of rare earth metal in organic synthesis.

EXPERIMENTAL

General procedure for the synthesis of *N*,*N*-diphenyl-α-cyanoamines: To a suspension of La(O-i-Pr)$_3$ (0.1 mmol, 10 mol%) in THF (5 mL) were added cinnamaldehyde (1 mmol) and dibenzylamine (1 mmol). After stirred at 40°C for 1 h, trimethylsilylcyanide (1.2 mmol) was added. The reaction mixture was stirred at 40°C for 10 h. Water was added and the product was extracted with diethyl ether. The organic layer was combined and dried with anhydride Na$_2$SO$_4$. After evaporated in vacuo, the residue was chromatographed on silica gel to afford the desired product with 78% yield.

Compound (1): M.p. 92–93°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.25$–7.59 (m, 15H), 4.91 (s, 1H), 3.88 (d, $J = 13.4$ Hz, 2H), 3.41 (d, $J = 13.4$ Hz, 2H). ^{13}C-NMR (CDCl$_3$): $\delta = 136.15$, 135.21, 131.35, 128.78, 128.73, 128.12, 128.55, 127.16, 126.58, 121.11, 114.37, 77.15, 76.89, 76.10, 55.38. MS: m/z (%) = 312 (M$^+$, 6), 91 (100), 286 (5), 235 (6). 221 (54), 194 (16), 149 (5), 116 (17), 65 (12). Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.57; H, 6.47; N, 8.97. Found: C, 84.48; H, 6.67; N, 8.75.

Compound (2): M.p. 112–113°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.24$–7.41 (m, 15H), 6.94 (d, $J = 16.1$ Hz, 1H), 6.08 (dd, $J = 4.3$, 16.1 Hz, 1H), 4.51 (m, 1H), 4.01 (d, $J = 13.6$ Hz, 2H), 3.43 (d, $J = 13.6$ Hz, 2H). ^{13}C NMR (CDCl$_3$): $\delta = 137.82$, 135.37, 134.75, 128.78, 128.72, 128.63, 128.54, 127.63, 126.78, 122.71, 115.37, 77.45, 77.03, 76.60, 55.28, 55.26. IR (KBr): $\nu = 3062$, 2920, 2228, 1494, 1377, 1295, 1123, 913, 739 cm^{-1}. MS: m/z (%) = 338 (M$^+$, 8), 91 (100), 311 (12), 247 (32), 220 (40), 222 (20), 142 (12), 115 (27), 65 (9). Anal. Calcd. for $C_{24}H_{22}N_2$: C, 85.21; H, 6.51; N, 8.28. Found: C, 84.98; H, 6.61; N, 8.15.

Compound (3): M.p. 91–92°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.48$ (d, $J = 0.52$, 2H), 6.90 (d, $J = 8.78$, 2H), 6.93–7.49 (m, 10H), 4.84 (s, 1H), 3.38 (d, $J = 13.4$ Hz, 2H), 3.87 (d, $J = 13.4$ Hz, 2H), 3.78 (s, 3H, OCH$_3$). ^{13}C-NMR (CDCl$_3$): $\delta = 137.75$, 135.27, 134.11, 128.56, 128.11, 128.32, 128.44, 127.15, 126.13, 121.14, 114.75, 77.78, 77.08, 75.80, 55.96. Anal. Calcd. for $C_{23}H_{22}ON_2$: C, 80.66; H, 6.49; N, 8.18. Found: C, 84.88; H, 6.61; N, 8.35.

Compound (4): M.p. 96–97°C. ^{1}H NMR (CDCl$_3$): $\delta = 8.31$ (d, $J = 8.83$, 2H), 7.82 (d, $J = 9.44$, 2H), 7.31–7.45 (m, 10H), 5.08 (s, 1H), 3.90 (d, $J = 13.34$ Hz, 2H), 3.51 (d, $J = 13.36$ Hz, 2H). ^{13}C NMR (CDCl$_3$): $\delta = 138.77$, 136.27, 135.75, 128.96, 128.32, 128.56, 128.43, 127.75, 126.12, 121.75, 114.14, 77.25, 77.07, 74.50, 55.21. Anal. Calcd. for $C_{22}H_{19}O_2N_3$: C, 73.92; H, 5.37; O, 8.95; N, 11.76. Found: C, 73.83; H, 5.16; N, 11.45.

Compound (5): M.p. 98–100°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.56$ (d, $J = 8.61$ Hz, 2H), 7.48 (d, $J = 8.45$ Hz, 2H), 7.05–7.36 (m, 10H), 4.67 (s, 1H), 3.69 (d, $J = 13.39$ Hz, 2H), 3.24 (d, $J = 13.34$ Hz, 2H). ^{13}C NMR (CDCl$_3$): $\delta = 138.66$, 137.27, 136.75, 129.76, 128.32, 128.66, 128.15, 127.14, 126.76, 121.65, 114.11, 78.10, 76.25, 74.10, 54.35. Anal. Calcd. for $C_{22}H_{19}N_3Br$: C, 73.92; H, 5.37; N, 11.76. Found: C, 67.52; H, 4.90; N, 7.16.

Compound (6): M.p. 93–95°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.35$–7.51 (m, 14H), 4.91 (s, 1H), 3.85 (d, $J = 13.3$ Hz, 2H), 3.31 (d, $J = 13.1$ Hz, 2H). ^{13}C NMR (CDCl$_3$): $\delta = 137.22$, 137.77, 136.15, 129.15, 128.33, 128.11, 128.75, 127.55, 126.65, 121.66, 115.12, 77.45, 75.15, 74.25, 53.01. Anal. Calcd. for $C_{21}H_{20}N_2$: C, 83.95; H, 6.72; N, 9.33. Found: C, 83.76; H, 6.57; N, 9.12.

Compound (7): M.p. 114–115°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.51$ (d, $J =$ 1.63 Hz, 1H), 7.31 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.03–7.32 (m, 10H), 4.57 (s, 1H), 3.61 (d, $J = 13.39$ Hz, 2H), 3.18 (d, $J =$ 13.34 Hz, 2H). ^{13}C NMR (CDCl$_3$): $\delta = 138.17$, 136.25, 134.88, 128.75, 128.22, 128.77, 127.50, 127.15, 77.25, 76.23, 76.15, 75.33, 74.21. Anal. Calcd. for $C_{22}H_{18}Cl_2N_2$: C, 69.29; H, 4.77; N, 7.35. Found: C, 69.11; H, 4.43; N, 7.16.

Compound (8): M.p. 86–87°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.15$–7.55 (m, 5H), 4.81 (m, 1H), 0.91–1.01 (m, 12H), 1.78 (m, 2H). Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.94; H, 8.07; N, 13.99. Found: C, 77.78; H, 7.92; N, 14.06.

Compound (9): M.p. 87–88°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.25$–7.55 (m, 5H), 4.81 (s, 1H), 2.51 (m, 4H), 1.61–1.46 (m, 6H). Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.94; H, 8.07; N, 13.9. Found: C, 77.78; H, 7.92; N, 14.06.

Compound (10): M.p. 111–112°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.21$–7.35 (m, 5H), 6.85 (d, $J = 15.58$ Hz, 1H), 6.02 (dd, $J = 3.1$ Hz, 15.3 Hz, 1H), 4.42 (m, 1H), 2.48 (m, 4H), 1.43–1.52 (m, 6H). Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.59; H, 8.03; N, 12.38. Found: C, 79.51; H, 7.92; N, 12.18.

Compound (11): M.p. 94–95°C. ^{1}H NMR (CDCl$_3$): $\delta = 7.52$ (d, $J = 8.31$ Hz, 2H), 7.38 (d, $J = 8.43$ Hz, 2H), 4.62 (s, $J = 3.1$ Hz, 15.3 Hz, 1H), 4.42 (m, 1H), 2.48 (m, 4H), 1.43–1.52 (m, 6H). Anal. Calcd. for $C_{13}H_{15}BrN_2$: C, 55.92; H, 5.43; N, 10.04. Found: C, 55.78; H, 5.23; N, 9.91.

Compound (12): M.p. 88–90°C. ^{1}H NMR (CDCl$_3$): $\delta = 1.66$ (m, 1H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.72 (d, $J = 6.1$ Hz, 3H), 3.82 (m, 1H), 3.61 (d, $J =$ 13.10 Hz, 2H), 3.21 (d, $J = 12.85$ Hz, 2H), 7.02–7.31 (m, 10H). Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.96; H, 7.98; N, 10.06. Found: C, 81.74; H, 7.68; N, 9.90.

Compound (13): M.p. 90–91°C. ^{1}H NMR ($CDCl_3$): $\delta = 7.02$–7.31 (m, 10H), 4.89 (s, 1H), 3.45 (d, $J = 13.60$ Hz, 2H), 1.15 (m, 3H). Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.31; H, 6.84; N, 11.86. Found: 81.11; H, 6.71; N, 11.91.

Compound (14): M.p. 97–99°C. ^{1}H NMR ($CDCl_3$): $\delta = 7.03$–7.31 (m, 5H), 4.58 (m, 1H), 7.53 (d, $J = 7.51$ Hz, 2H), 7.42 (d, $J = 8.10$ Hz, 2H), 3.45 (d, $J = 13.25$ Hz, 2H), 1.14 (m, 3H). Anal. Calcd. for $C_{16}H_{15}BrN_2$: C, 60.96; H, 4.81; N, 8.89. Found: C, 60.76; H, 4.61; N, 8.61.

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