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Aluminum Trichloride-Promoted Aminolysis of Cyclic Imides and Oxazolidinones.

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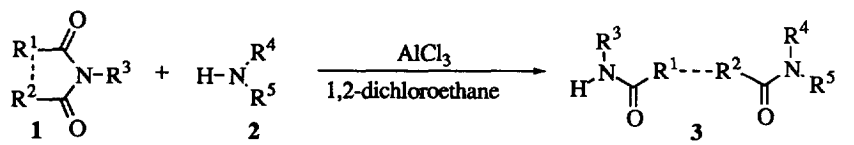
Abstract: *Aluminum trichloride promotes the nucleophilic ring-opening reaction of cyclic imides and oxazolidinones with amines.*

The ring-opening reactions of cyclic imides by nucleophiles provide an attractive route to ω-functionalized amides. However, except for phtalimide,[1] this reaction occurs under rather drastic experimental conditions or using strong nucleophiles. For example, alcoholysis requires high temperature (200°C) and aminolysis is only applicable to ammonia or methylamine (T>100°C).[2]

We have recently reported that transamidation reactions and aminolysis of lactams proceeded in high yield at room temperature, even with weakly basic or sterically hindered amines, in the presence of a small excess of aluminum trichloride.[3] It was thus tempting to extend this Lewis acid-promoted ring-opening reaction to cyclic imides (Scheme 1) and oxazolidinones, and here we report our preliminary results.

Scheme 1.



1 **2** **3**

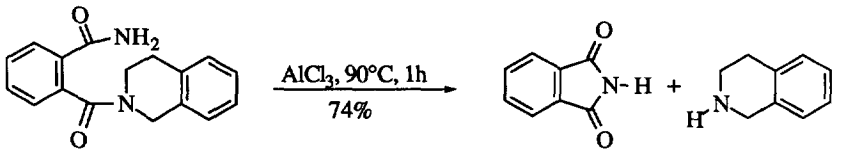
In a typical experiment, the amine **2** (12.5 mmol) is added to a suspension of aluminum trichloride (6.5 mmol) in 1,2-dichloroethane (10 mL) at 0°C . The reaction mixture is allowed to warm to room temperature and a 1,2-dichloroethane solution (10 mL) of the cyclic imide **1** (5 mmol) is added dropwise. The mixture is stirred at room temperature or 90°C (see Table 1), and monitored by TLC. A mixture of ice and water (50 mL) is added and the organic phase collected, washed with brine, and dried ($MgSO_4$). The products are isolated by

chromatography on silica gel using $CHCl_3$/MeOH (95/5) as eluent.

As shown in Table 1, a variety of *N*-H or *N*-substituted cyclic imides reacts with secondary aliphatic or aromatic amines to afford the desired ring-opened products **3** in good to excellent yield. In none of the reactions examined did aminolysis occur in the absence of $AlCl_3$.

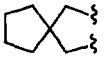
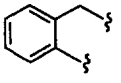
With 1,2,3,4-tetrahydroisoquinoline (THIQ) the reaction usually takes place at room temperature. However, in the case of the spiro amide (entry c), heating to 90°C is necessary, probably due to steric factors, while with the homophtalimide the reaction fails to occur (entry e), possibly because of the stability of the enol form. Note that the temperature is an important reaction parameter since at high temperature recyclisation of the initally formed ω-bis(amides) can occur, giving back the cyclic imide as exemplified in Scheme 2.

Scheme 2.



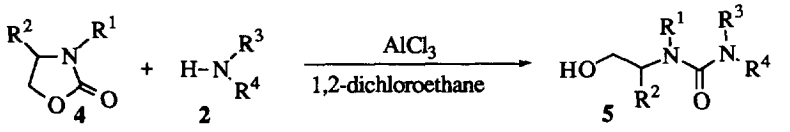
More vigorous conditions are required if the nitrogen atom is substituted (entries a-b and f-g), but even the presence of the bulky cyclohexyl group does not lower the yield. The result obtained with the weakly basic *N*-methylaniline (entry h) is noteworthy, and shows the wide applicability of this Lewis-acid promoted ring-opening method.

Table 1. Aluminum Trichloride-Promoted Aminolysis of Cyclic Imides **1**.[5]

Entry	R^1----R^2	R^3	R^4	R^5	**1**/2/$AlCl_3$	Temp (°C)/ Time (h)	Yield [%]	m.p. (°C)
a	$-(CH_2)_2-$	H	THIQ		1/2.5/1.3	25/16.5	79	124
b	$-(CH_2)_3-$	H	THIQ		1/2.5/1.3	25/19.0	65	61-63
c		H	THIQ		1/2.5/1.3	90/17.0	68	oil
d		H	THIQ		1/2.5/1.3	25/3.0	85	143
e		H	THIQ		1/2.5/1.3	90/16.0	-	-
f	$-(CH_2)_2-$	CH_3	THIQ		1/3.5/2.3	90/4.0	74	oil
g	$-(CH_2)_3-$	*c*-hex	THIQ		1/3.5/2.3	90/15.0	76	125-127
h	$-(CH_2)_2-$	H	Ph	CH_3	1/2.5/1.3	25/16.5	79	124

Since, in marked contrast to lactams, the presence of an electron-withdrawing group at the nitrogen atom is not necessary,[3a,b,4] the next question was whether the aluminum trichloride-promoted aminolysis could be applied to unactivated oxazolidinones. As shown in Table 2, *N*-H oxazolidinones **4** react with THIQ at 90°C giving rise to ω-hydroxy-ureas **5** in good yield, whereas *N*-methyl oxazolidinone is inert (entry c).

Table 2. Aluminum Trichloride-Promoted Aminolysis of Oxazolidinones **4**.[5]

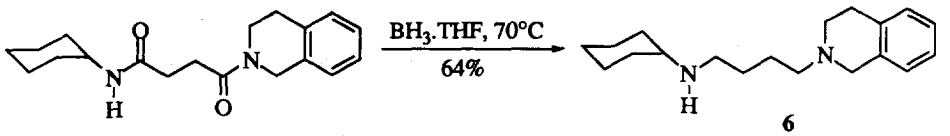


4 **2** **5**

Entry	R^1	R^2	R^3 R^4	**4/2**/$AlCl_3$	Temp (°C)/ Time (h)	Yield [%]	m.p. (°C)
a	H	H	THIQ	1/2.5/1.3	90/16.0	88	105-106
b	H	CH_2Ph	THIQ	1/2.5/1.3	90/15.0	70	126-128
c	CH_3	H	THIQ	1/2.5/1.3	90/18.5	-	-

In conclusion, the aluminum trichloride-promoted aminolysis of cyclic imides and oxazolidinones is a useful method for the preparation of unsymmetrical ω-bis(amides) and ω-hydroxy-ureas. In addition to their biologic interest,[6] these derivatives are useful synthons as illustrated by the preparation of the unsymmetrical ω-bis(amine) **6** (Scheme 3).

Scheme 3.



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References and Notes

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5. All new compounds afforded analytical data in accordance with their structures. *For examples:*
N-(3,4-dihydro-1*H*-isoquinolin-2-yl)-(3,3-tetramethylen)-glutarylamide (Table 1, entry c): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.28-1.55 (8H, m, $C(CH_2)_4$), 2.18 (1H, s, CH_2CONH_2), 2.19 (1H, s, CH_2CONH_2), 2.35 (1H, s, $(CH_2)_2NCOCH_2$), 2.38 (1H, s, $(CH_2)_2NCOCH_2$), 2.74 (1H, t, J = 5.9 Hz, CH_2CH_2N), 2.83 (1H, t, J = 5.9 Hz, CH_2CH_2N), 3.62 (1H, t, J = 5.9 Hz, CH_2CH_2N), 4.00 (1H, t, J = 5.9 Hz, CH_2CH_2N), 4.56 (1H, s, $CH_2NCH_2CH_2$), 4.89 (1H, s, $CH_2NCH_2CH_2$), 7.03 (6H, m, $H_{arom.}$ and NH_2); ^{13}C-NMR ($CDCl_3$, 50.323 MHz) δ 23.88 (CCH_2CH_2), 28.06 (CH_2CH_2N), 28.99 (CH_2CH_2N), 37.86 $(CH_2)_2NCOCH_2$), 38.12 (CCH_2CH_2), 41.74 (CH_2CONH_2), 42.25 (CH_2CH_2N), 43.89 (CH_2CH_2N), 46.32 ($CH_2NCH_2CH_2$), 47.67 ($CH_2NCH_2CH_2$), 77.44 ($C(CH_2)_4$), 125.87 ($C_{arom.}$), 126.25 ($C_{arom.}$), 126.57 ($C_{arom.}$), 126.64 ($C_{arom.}$), 126.39 ($C_{arom.}$), 127.06 ($C_{arom.}$), 127.69, ($C_{arom.}$) 128.44 ($C_{arom.}$), 131.48 ($C_{arom.}$), 132.73 ($C_{arom.}$), 133.60 ($C_{arom.}$), 134.71($C_{arom.}$), 170.73 ($CONH_2$), 182.10, (CO), 182.33. (CO) ; IR (1,2-dichloroethane) 3407, 3311 cm^{-1} (NH_2), 1658 cm^{-1} (CO), 1587 cm^{-1} (C=C); Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.87; H, 8.10; N, 9.24.
N-(3,4-dihydro-1*H*-isoquinolin-2-oyl)-2-benzyl-ethanolamine (Table 2, entry b): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.71-2.88 (4H, m, CH_2Ph and CH_2CH_2N), 2.42-3.72 (4H, m, CH_2OH and CH_2CH_2N), 4.00 (1H, m, $CHCH_2$), 4.38 (2H, m, $CH_2NCH_2CH_2$), 4.76 (1H, d, J = 6.7 Hz, NH), 6.98-7.28 (9H, m, H_{arom}); ^{13}C-NMR ($CDCl_3$, 50.323 MHz) δ 28.71 (CH_2CH_2N), 37.33 (CH_2CH_2N), 41.10 ($CHCH_2$), 45.26 ($CH_2NCH_2CH_2$), 54.09 ($CHCH_2$), 65.31 (CH_2OH), 126.11 (C_{arom}), 126.22 ($C_{arom.}$), 126.54 ($C_{arom.}$), 127.08 ($C_{arom.}$), 128.13 ($C_{arom.}$), 128.47 ($C_{arom.}$), 129.08 ($C_{arom.}$), 133.01, ($C_{arom.}$) 134.78 ($C_{arom.}$), 137.83 ($C_{arom.}$), 157.93 (CO); IR (1,2-dichloroethane) 3609 cm^{-1} (OH), 3446 cm^{-1} (NH_2), 1631 cm^{-1} (CO), 1584 cm^{-1} (C=C); Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.68; H, 7.10; N, 9.14.

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