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BORON TRICHLORIDE CATALYZED ORTHO CARBONYLATION OF PHENOLS: SYNTHESIS OF 2-HYDROXY-ARYL-CARBOXYAMIDES AND -KETONES.[1]

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Abstract: In the presence of equimolar quantity of BCl_3, phenols 1 react with isocyanates and acyl chlorides to give, usually with good-excellent yields, 2-hydroxy-aryl-carboxy-amides 2 and 2-hydroxy-aryl-ketones 3 respectively. A distinctive behaviour of BCl_3 in comparison with other Lewis acids is observed.

Recently we reported a facile synthesis of racemic and optically active (2-hydroxy-aryl)-glycolic acid derivatives via a Lewis acid catalyzed aldolic condensation of phenols 1 and 2-keto esters.[2,3]

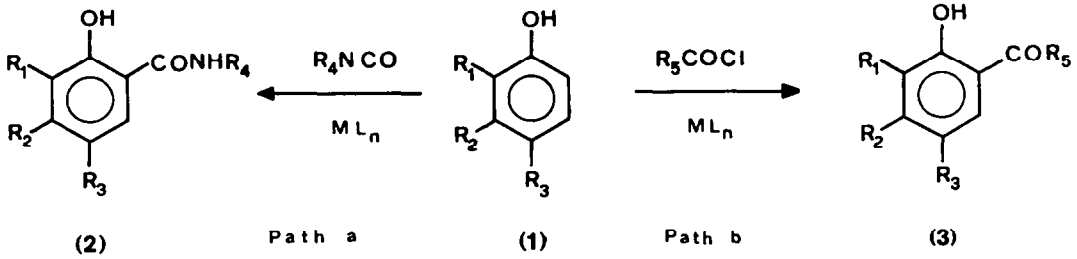
The highly efficient formation of ortho substituted phenolic compounds and the easy adopted experimental procedure (one-pot synthesis) encouraged us to continue our investigation with the aim of developing other useful industrial routes to 2-hydroxy-aryl derivatives.

The importance of ortho-hydroxy-aryl-carboxyamides 2 and -ketones 3 as pharmaceutical products or as intermediates in drugs preparation is well known.[4]

We decided to reexamine a previous study[5] on the preparation of compounds 2 and find an alternative route[6] to compounds 3. The synthesis of some peculiar derivatives 3, obtained in an indipendent and contemporaneous work, has been published very recently.[7,8]

Here we report the results of the reaction of phenols 1 with alkyl (aryl) isocyanates (**Scheme 1**, path a) and with acid chlorides (**Scheme 1**, path b) to give compounds 2 and 3 respectively. Initially we tested the possibility of preparing N-substituted salicylamides 2 by Lewis acids catalyzed direct condensation of

SCHEME 1



(2) Path a (1) Path b (3)

Table 1. Lewis acid catalyzed condensation of phenol and n.butylisocyanate, $R_4N=C=O$ (R_4=n.C_4H_9). [a]

Lewis acid	recov. phenol (%)	g.l.c. evaluated yield (%)	
		2b	N-n.butylphenylcarbamate
$AlCl_3$	10	4	80
BCl_3	<5	89	2
$BF_3{\cdot}Et_2O$ [b]	20	4	7
$SnCl_4$	65	1	n.d. [c]
$TiCl_4$	22	11	n.d.
$ZrCl_4$	100	--	--

[a] General reaction conditions: to a solution of phenol (21 mmol) in toluene (50 ml) 21 mmol of Lewis acid and, after 10 min., 21 mmol of n-butylisocyanate were added; the mixture was refluxed, under nitrogen, for 12 hr, hydrolysed with 10% HCl, and g.l.c.-analysed (2m x OV 3%, programmed temperature 180-240°, heating rate 10°/min) [b] Mixture of other unidentified products was found. [c] Not determined.

Table 2. Boron trichloride catalyzed synthesis of N-substituted salicylamides (2).

Compound (2)	R_1	R_2	R_3	R_4	method [a]	isol. yield (%)	m.p. °C (b.p. °C/ /mmHg	m.p. °C (b.p.°C/ /mmHg) [b]
a	H	H	H	CH_3	A,B	70-78	88-9 [c]	89
b	H	H	H	C_4H_9	C	89	(151/3)	(153-6/3)
c	H	H	H	C_6H_5	C	90	134-5 [d]	136
d	H	H	H	p.ClC_6H_4	C	93	169-70 [c]	- [e]
e	H	H	H	o.$CH_3C_6H_4$	A	86	143-4 [d]	144
f	H	H	H	1-$C_{10}H_7$	A	84	185-6 [d]	187
g	H	OCH_3	H	CH_3	B	75	138 [f]	- [g]
h	H	H	CH_3	CH_3	B	70 [h]	123-4 [i]	- [j]
i [k,l]	H	Cl	H	CH_3	B	40	138-40 [c]	- [m]
j [n]	H	Cl	H	C_6H_5	C	75	217-20 [d]	- [o]

[a] Methods A,B and C differ for the used catalyst [commercial 1M solution of BCl_3 in CH_2Cl_2 (methods A and B) and pure liquid BCl_3, dissolved in toluene (method C)] and for the work-up (see exp. part); [b] Beilsteins Handbuch der Organischen Chemie and loc. ref.; [c] from n.hexane/diethyl ether 7/3; [d] from ethanol 95%; [e] $C_{13}H_{10}ClNO_2$ [element analysis found (calc.) : C 63.10 (63.04), H 4.08 (4.07), N 4.02 (4.04)]; [f] from toluene; [g] $C_9H_{11}NO_3$: C 59.80 (59.66), H 6.15 (6.12), N 7.85 (7.73); [h] 20% of unreacted compound 1h; [i] from n.hexane/ethyl acetate 7/3; [j] $C_9H_{11}NO_2$: C 65.51 (65.44), H 6.75 (6.71), N 8.52 (8.48); [k] 35% of unreacted compound 1i; [l] 10% of isomeric N-methyl (1-hydroxy-5-chloro)-salicylamide [m.p. 182°; el.anal.: $C_8H_8ClNO_2$: C 51.81 (51.77), H 4.35 (4.34), N 7.61 (7.55); IR (cm^{-1}): 3320,3140,1630,915; ^{1}H-NMR (300 MHz)($CDCl_3$/TMS)(δ,ppm): 11.90(b,1H;OH), 7.58(b,1H,NH), 7.22(d,d,1H,H_5, J=8.4Hz, J=1.2Hz), 6.92(d,d,1H,H_4), 6.88(d,d,1H,H_6), 3.05(d,3H,CH_3); M.S.(m/e; rel. int. %): 185(M^+,100), 156(88)]; [m] $C_8H_8ClNO_2$: C 51.86(51.77), H 4.40(4.34), N 7.57(7.55); [n] 9% of isomeric N-phenyl (1-hydroxy-5-chloro)-salicylamide [m.p. 117°; el. anal. $C_{13}H_{10}ClNO_2$: C 63.00(63.04), H 4.12(4.07), N 4.06(4.04); IR(cm^{-1}): 3320,3160,1635,915; ^{1}H-NMR (90 MHz)($CDCl_3$/TMS)(δ,ppm): 12.23(b,1H,OH), 9.17 (b,1H,NH), 7.95-6.95(m,8H,arom.H); M.S.(m/e; rel. int. %): 274(M^+,9), 93(100)]; [o] $C_{13}H_{10}ClNO_2$: C 62.90(63.04), H 4.12 (4.07), N 4.03(4.04).

phenolic compounds and isocyanates avoiding the use of preformed alkaline phenolates.[5] In **Table 1** are reported the results of different catalysts in a model reaction, i.e. the condensation of phenol with N-n.butyl isocyanate. $TiCl_4$, that we had found to be the best catalyst in the reaction of phenols and 2-keto esters,[2,3] afforded in this case a poor result; $ZrCl_4$ and $SnCl_4$, under the same conditions, were practically inert while $AlCl_3$ gave a good yield in O-acylation product. On the contrary BCl_3 (but not BF_3Et_2O) showed high stereospecificity (C-acylation vs. O-acylation), regioselectivity (ortho vs. para position) and excellent yield. The influence of different substituents on the aromatic ring and on the isocyanate moiety was verified, obtainig usually analogous good-excellent results (**Table 2**); only t.butylisocyanate did not react under the same experimen-

Table 3. Spectroscopic and mass spectrum data of compound **2**.

Compound 2	^{1}H-NMR (90 MHz) ($CDCl_3$/TMS)(δ,ppm)	IR (cm^{-1})	M.S.(m/e)rel.int. %
a	8.70(s,1H,OH),7.60-7.20(m,2H,arom.H) 7.15-6.80(m,2H,arom.H),6.50(b,1H,NH) 3.05(d,3H,CH_3)	3410,1645	151(M^+,100),121(90)
b	12.40 (b,1H,OH), 7.50-6.70 (m,4H, arom. H), 6.45(b,1H,NH), 3.45(q,2H, CH_2N),1.80-1.20(m,4H,$(CH_2)_2$), 0.97 (t,3H,CH_3)	3300,1592	193(M^+,32),121(100)
c	12.00(b,1H,OH),7.95(b,1H,NH), 7 60--6.50(m,9H,arom.H)	3300,1620	213(M^+,20),121(30), 93(100)
d	11.80(b,1H,OH),8.10(b,1H,NH), 7.60--7.20(m,6H,arom.H), 7.10-6.80 (m,2H arom.H)	3320,1624	247(M^+,20),126(100) 120(60)
e	11.90 (b,1H,OH),8.00(b,1H,NH),7.50--6.40 (m,8H,arom.H),2.33(s,3H,CH_3)	3318,1625	227(M^+,14), 93(100)
f	11.90(b,1H,OH),10.60((b,1H,NH), 8.20--6.90(m,11H,arom.H)	3322,1630	263(M^+,35),143(100) 121(34)
g	11.80(b,1H,OH),8.50(b,1H,NH), 7.35 (d,1H,arom.H),7.00-6.30(m,3H,arom.H) 3.80(s,3H,OCH_3),2.95(d,3H,NCH_3	3410,1650 1596	181(M^+,71),151(100)
h	12.50 (b,1H,OH), 7.40-6.40 (m,4H, arom.H,NH),3.05(d,3H,NCH_3), 2.25 (s,3H,CH_3)	3400,1648 1596	165(M^+,80),134(100)
i [a]	12.10(b,1H,OH)8.10(b,1H,NH), 7.34(d, 1H,H_3),6.96(d,1H,H_6),6.78(d,d,1H,H_4, J=8.4 Hz,J=2 Hz), 2.99(d,3H,CH_3)	3415,1650 1590	185(M^+,74),155(76), 151(100)
j	12.50(b,1H,OH),10.78(b,1H,NH), 8.20--7.00(m,8H,arom.H)	3410,1640 1610	274(M^+,13),155(19), 93(100)

[a] 300 MHz.

Table 4. Lewis acids catalyzed synthesis of o.acylphenols **3**.[a]

R_1	R_2	R_3	R_5	Lewis acid	react.time (h)	isol.yield (%) **3**	m.p.°C (lit.)
H	H	H	C_6H_5	BCl_3 [b]	24	/	/
H	OCH_3	H	C_6H_5	BCl_3	10	85	65(66) [c,d]
H	OCH_3	H	C_6H_5	$TiCl_4$	14	77 [e]	65
H	OCH_3	H	p.$CH_3C_6H_4$	BCl_3	10	80	95(98) [f,g]
H	OCH_3	H	p.$CH_3C_6H_4$	$TiCl_4$	14	73 [e]	95

[a] Reactions were carried out in benzene at reflux temperature (see exp. part); [b] also in methylene chloride at 40°C and in decaline at 110°C no product was formed after 24 h; [c] from i.propanol; [d] Merk Index X Ed. 1983, **OXYBENZONE** N° 6822; [e] demethylated product was also obtained; [f] from benzene; [g] C. Perrot, E. Cerutti, Bull. Chem. Soc. France, **1974**, 2225; Merck Index, **MEXENONE**, N° 6045.

tal conditions and more than 70% of the starting phenol was recovered. In the case of 3-chloro-phenol, both ortho reaction products were observed and obtained, the molar ratio of the less hindered (1,2,5)-derivative (**2i** or **2j**) on the more hindered (1,2,3)- isomer being 4 or 8. The catalysts used were either a commercial 1 M solution of BCl_3 in methylene chloride (method A), or a mixture of it with benzene (method B), or the pure BCl_3 freshly dissolved in toluene (method C). The last catalyst was shown to be slightly more efficient in comparative reactions. The hydrolysis procedure was accomplished in different ways (see experimental section) depending on the stability and the solubility of intermediate boron heterocycle. For the synthesis of compounds **3**, we were looking for a general method that was alternative to Fries rearrangement,[6] independent from the structure of the acylating agent[7,8] and industrially feasible. The comparison between different Lewis acids was limited in this case to BCl_3 and $TiCl_4$ on the basis of our previous work[2] and of the present results with isocyanates. With reactive phenols, but not with simple phenol (at least with benzoyl chloride), BCl_3 appears an excellent and very regioselective catalyst in the reaction with different acylating agents and working at different temperature (**Table 4** and 5). $TiCl_4$, on the contrary, gives usually mixtures of C- (ortho and para) and O-acylation products or by-products and its behaviour is not predictable depending either on the structure of acyl chlorides or on the reaction temperature. Only the reaction of 1-NpOH with mono chloro mono methyl ester of oxalic acid gave a satisfactory result in ortho acylation (**Table 5**), due to the possible interaction of the carbalkoxy group with titanium, bonded to phenolic and carbonyl oxygen atoms, that should stabilize the transition state complex.[3]

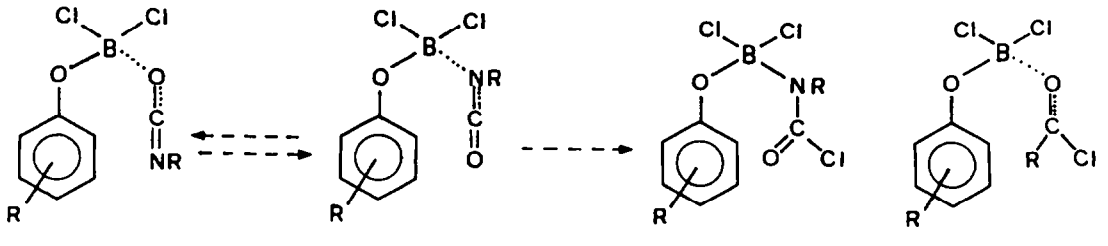
Discussion: The reported results show the synthetic utility of our simple, one-pot procedure for the ortho functionalization of phenolic compounds with isocyanates and acyl chlorides. By comparison with the previous and parallel works in this area,[5,7,8] we have established that BCl_3 is the choice catalyst in the synthesis of derivatives **2**, usually without any limitation on the nature of isocyanate, alkyl and aryl isocyanates giving similar and good results, and appear alternative andindustrially more convenient for the preparation of compounds **3**. The relatively high reaction temperature (>60°C), for best yields, suggest that the reactive specie should be ArO_xBCl_y (x=1, y=2 as first hypothesis), that of course may be in equilibrium with other boron phenoxy complexes. This specie does not react easily with electrophiles reagents but can afford aldolic type condensation products after coordination with compounds containing C=X bond (X= O or NR); the fact that $(C_6H_5O)_xBCl_y$ is able to react with isocyanates but not with a simple acyl chloride, such as benzoyl chloride, could be due, in the former case, to a higher polarizability of the C=X bond and/or to the best coordination of the two reaction partners through a N-B bond (**Figure**). The latter hypothesis might also justify the negative result with t.butyl isocyanate, where the hindering t.butyl group should destabilize a similar intermediate. It is then to underlinie that 4-oxo-3,4-dihydro-2H-(benzo-1,3,2-oxazaboranes) have been recovered by condensation of salicylamides with aryl dihydroxy boranes by heating in aromatic solvents with azeotropic removal of water,[9] and that there are some evidences on the formation of carbamoyl halides in the reaction between isocyanates and metal halides after the insertion of the nitrogen atom on the metal halide bond.[10] Our work shows numerous analogies with researches of Sugasawa and coworkers. They have in fact used equimolar quantity of BCl_3 in the condensation of phenols with chloroacetonitrile,[11] which affords, after hydrolysis, o.hydroxyaryl chloromethylketones, and in the ortho functionalization of anilines via condensation with carbonyl com-

Table 5. Reaction of 1-naphthol (R_1,R_2=(CH=CH)$_2$; R_3=H) and acid chlorides in the presence of Lewis acids.

R_5	Lewis acid	Solvent	T°C	reaction time (h)	isol.yield	m.p.°C(lit.)
C_6H_5	BCl_3	CH_2Cl_2	25	12	70	64-5(65) [a]
$C_6H_5CH=CH$	BCl_3	CH_2Cl_2	25	20	63	127-8(129) [a]
$C_6H_5CH=CH$	BCl_3	C_6H_5	80	5	80	128
$CH_3CH=CH$	BCl_3	CH_2Cl_2	25	0.5	73	87 [b]
OCH_3	BCl_3	CH_2Cl_2	25	15	85	75-6(76-8) [a]
$C_6H_5CH=CH$	$TiCl_4$	$Cl_2CHCHCl_2$	25	0.5	20 [c]	128
$C_6H_5CH=CH$	$TiCl_4$	$Cl_2CHCHCl_2$	110	0.5	20 [c]	128
$(CH_3)_2C=CH$	$TiCl_4$	CH_2Cl_2	0	3	45 [d]	105-6 [e]
$(CH_3)_2C=CH$	$TiCl_4$	$Cl_2CHCHCl_2$	110	5	76	105-6
$COOCH_3$	$TiCl_4$	CH_2Cl_2	-40	0.2	90	92-3 [f]

[a] Beilstein Handbuch der Organischen Chemie and loc. ref.; [b] el. anal. $C_{14}H_{12}O_2$: C 79.25(79.22), H 5.68(5.70); IR(cm^{-1}): 1690, 1660; ^{1}H-NMR (CDCl3/TMS)(δ,ppm): 14.92(b,1H,OH), 8.25(m,1H,H_8), 7.80-6.85 (m,6H,arom.H,COCH=), 5.95(m,1H,=CHCH$_3$), 1.90(m,3H,CH$_3$); M.S.(m/e; rel. int. %): 212(M^+,19), 171(52), 130(100); [c] 50% of isomeric (1-hydroxy-4-naphthyl)COR$_5$[m.p. 168-9°C; IR: 3300, 1630; ^{1}H-NMR: 8.10--7.10(m,13H,OH,arom.H,COCH=), 6.75 (d,1H,=CHC$_6$H$_5$); M.S.: 274 (M^+,42), 170 (100)] and 10% of 1-NpOCOR$_5$ [m.p. 109-110°C; IR: 1725, 1630; ^{1}H-NMR: 8.02-7.20(m,13H, arom.H,COCH=), 6.08(d,1H,CHC$_6$H$_5$); M.S.: 274(M^+,6), 131(100)] [d] 14% of isomeric (1-hydroxy-4-naphthyl)COR$_5$ [m.p. 142-3°C; IR: 3250, 1690, 1640; ^{1}H-NMR: 8.70 (m, 1H,H_5), 8.30 (m,1H,H_8), 7.70-6.80 (m,4H,arom.H), 6.55 (m,1H,COCH=), 5.70 (b,1H, OH), 2.15 (s,3H,CH$_3$), 1.97 (s,3H,CH$_3$); M.S.: 226(M^+,80), 211(65), 209(65), 170(100)] and 39% of 1-NpOCOR$_5$ [IR: 1740, 1643; ^{1}H-NMR: 8.00-7.10(m,7H,arom.H), 6.07(m,1H,COCH=), 2.22(s,3H,CH$_3$), 1.97(s,3H,CH$_3$); M.S.: 226(M^+,35), 144(100), 115(50)] ; [e] el. anal. $C_{15}H_{14}O_2$: C79.60(79.62), H 6.25(6.24); IR: 1625, 1580; ^{1}H-NMR: 15.20(b,1H,OH), 8.43(m,1H,H_8), 7.80-7.12(m,5H,arom.H), 6.80(m,1H,COCH=), 2.20(s,3H,CH$_3$), 2.00(s,3H,CH$_3$); M.S.: 226(M^+,18), 211(100); [f] el. anal. $C_{12}H_{10}O_3$: C 71.34(71.28), H 5.00(4.98); IR: 1742, 1640; ^{1}H-NMR: 13.20(b,1H,OH), 8.50 (m,1H,H_8), 7.90-7.30(m,5H,arom.H), 4.05(s,3H,CH$_3$); M.S.: 230(M^+,3), 202(23), 170 (100).

FIGURE



pounds.[12] It is to note, however, that these authors consider indispensable the presence of $AlCl_3$ in 0.1-1 mole equivalent as cocatalyst for both reactions. In the cases they have studied, the coordination with the metal must obviously occur through the formation of a N-B bond. The different behaviour between boron and alluminium catalysts, at least with aliphatic isocyanates (**Table 1**)(see also ref. 5), and between boron and titanium catalysts in the acylation reactions can't be, at the present, rationalized in a cut way either because the structure of different intermediate complex(es) could vary with the metal or because the different lenghts and polarizabilities of M-O and M-N bonds (M=metal) could cause a different evolution or prevent the formation of proper metal intermediate complex(es). However, because we obtained the same yields in the boron trichloride catalyzed reaction of methyl isocyanate either with phenol or with sodium phenolate (prepared by reacting phenol and NaH), in benzene at 60°C, we can say that, at least in the synthesis of compounds **2**, HCl, that is evolved during the formation of reactive specie(s) ArO_xBCl_y, does not influence the course of the reaction.

Experimental

General: All compounds used were commercially available (chem. purity >98%). BCl_3 was used as 1 M CH_2Cl_2 solution (Aldrich)or neat(Merck). Solvents were purified as usual and stored on molecular sieves. Three general procedures (A, B and C) were adopted for the synthesis of compounds **2** and are exemplified for the preparation of N-methyl salicylamide **2a** (methods A and B) and for N-(p.chlorophenyl) salicylamide **2d** (method C); compounds **2a, c, d, e, f, g, h** were purified by crystallization of the crude reaction product, compound **2b** was bulb to bulb distilled on a Buchi GKR-50 Kugelrohr apparatus, compounds **2i** and **2j** and the corresponding isomers were purified by column cromatography and then recrystallized. A general procedure was adopted for the preparation of compounds **3**.
M.p. were determined on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer E-177 spectrometer. Mass spectra were obtained on Perkin-Elmer RMU-6D or VG ZAB spectrometers at 70 eV. ^{1}H-NMR were recorded on Varian A 90 or on Brucker 300 spectrometers. Analytical TLC or HPTLC were performed on precoated Merck Silica gel 60 plates with QF-254 indicator, usually using n.hexane/ethyl acetate blends. Flash cromatography was performed using Woelm 32-63 mμ silica gel. Isomer distribution was determined by quantitative densitometry of HPTLC plates, at 254 nm, on a CAMAG 76510 photodensitometer. Elemental analyses were performed at the University of Milan.
Synthesis of compound **2a** (method A): To 20 ml (20 mmol) of a 1M CH_2Cl_2 solution of BCl_3, cooled at -10° and under nitrogen, a solution of 1.8 g (20 mmol) phenol in CH_2Cl_2 (10 ml) was added. 1.2 g (20 mmol) methyl isocyanate was then slowly injected into the mixture through a rubber septum. The solution was heated under reflux for 6 h. At the end of the reaction, as determined by T.L.C., the cooled solution (at 0°) was slowly added to a mixture of 100 ml 5% HCl and 60 ml diethyl ether and left, under stirring, for 2h at room temperature. The aqueous layer was separated and extracted with ether (3 x 30 ml); the combined organic layer was washed with NaCl saturated solution (50 ml) and concentrated. The crude product was crystallized from n.hexane/diethyl ether (7/3) to give 2.3g (c.y.76%) of **2a**.
Synthesis of compound **2a** (method B): To 20 ml (20 mmol) of a 1M CH_2Cl_2 solution of BCl_3, cooled at -10° and under nitrogen, a solution of 1.8 g (20 mmol) phenol in benzene (30 ml) was added. A solution of 1.2 g (20 mmol) methyl isocyanate in benzene (20 ml) was slowly added at 0°. The resulting homogeneous solution was heated under reflux for 4h. At the end of the reaction, the solution was cooled at 0° and quenched with 10% NaOH (100 ml). The aqueous layer was separated, acidified with 10% HCl and the product extracted with benzene. After removal of the solvent and crystallization, 2.2 g (c.y. 73%) of **2a** was recovered.
Synthesis of compound **2d** (method C): 2.4 g (20 mmol) BCl_3 was dissolved in toluene (35 ml) at -10° and this solution was slowly added, under nitrogen, to 1.8 g. (20 mmol) phenol in toluene (20 ml). 3.7 g (20 mmol) p.chlorophenylisocyanate was then added at room temperature and the mixture was refluxed for 16 h. At the end of the reaction, ethylene glycol (20 ml) was added at room temperature and toluene distilled off to give an homogeneous solution. Water (14 ml) was added to the hot mixture, that was then allowed to cool slowly at room temperature. The solid product was filtered, washed with water and dried under vacuum. After crystallization from n.hexane/diethyl ether (7/3), 4.5 g (c.y. 93%) of **2d** was obtained.
General procedure to prepare compound **3**: The Lewis acid (20 mmol) was dissolved in the reported solvent (20 ml) usually at -10°. A solution of compound **1** (20 mmol)in the same solvent (30 ml) was then added, under nitrogen, followed by 20 mmol of

the acyl chloride. The reaction temperature was adjusted, as reported in **Table 4** and 5, and the mixture was allowed to run for the requested time. After quenching with 10% HCl at room temperature, the mixture was stirred for 1h. The aqueous phase was separated and extracted with the same organic solvent. The combined organic layer was washed with water, dried and concentrated. The product was purified and recovered by flash cromatography and the crude mixture quantitatively analyzed by densitometry. Where reported (**Table 4**), the product 3 was also crystallized.

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