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Chemoselective CaO-Mediated Acylation of Alcohols and Amines in 2-Methyltetrahydrofuran

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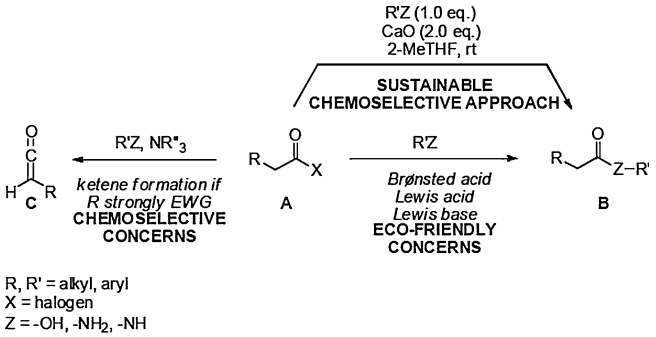
Calcium oxide is proposed as an innocuous acid scavenger for the chemoselective synthesis of amide- and ester-type compounds. Although these molecules have wide spread applications in organic and pharmaceutical chemistry, and a large number of routes have been designed for their synthesis, the development of more efficient and environmentally friendly acylation strategies remains an ongoing challenge. The use of CaO allows for the stoichiometric acylation of primary alcohols in the presence of phenols or tertiary alcohols; amines can also be subjected to acylation reactions in the presence of hydroxyl groups. Chirality is obtained through acylation if the starting material is an optically pure alcohol or if a chiral acylating agent is used. Furthermore, the use of 2-methyltetrahydrofuran (2-MeTHF), a more ecofriendly solvent, leads to maximized yields. This protocol is successfully applied to the synthesis of an interesting *N*-aryloxazolidin-2-one intermediate for the preparation of linezolid-type compounds.

Introduction

Ester and amide moieties are ubiquitous in nature;[1,2] they are often encountered both in physiologically relevant structures (e.g., acetylcholine, peptides) and in biologically active molecules (e.g., acetylsalicylic acid, paracetamol, and dextromoramide).[3] Because of this widespread importance, acylation-type reactions continue to be an exciting research field in view of designing efficient and environmentally acceptable synthetic processes that can be easily scaled-up for industrial purposes.[4,5] Generally, acylations are performed by treating an appropriate carboxylic acid derivative (acyl halide, anhydride, ester) with alcohols or amines in the presence of a suitable activator (Scheme 1).[1]



Scheme 1. Acylation procedure for alcohols and amines.

The procedure involving acylation through acid halides offers the clear advantage of atom efficiency compared to the use of other acylating agents (e.g., anhydrides). As observed by Strazzolini et al., the need for such an activator in esterification reactions is explained by competition between alkyl halide and ester formation.[6] Esterification reactions in the absence of activators are not fully understood and have limited substrate scope (aromatic acid chlorides or compounds with α-acidic hydrogens are not used); this may be attributed to a considerable excess of the required acyl donor.[7] These limitations stimulated efforts to develop activators for improving the reactivity, among the most common are Brønsted acids (e.g., HCl,[8] p-TsOH[9]) and Lewis acids (e.g., $CeCl_3$,[10] $MgBr_2$,[11] $ZrCl_4$,[12] $Sc(OTf)_3$,[13] $LiClO_4$,[14] $Mg(ClO_4)_2$[15]). These acids cannot be used in the presence of acid-sensitive substrates, thus reducing their real usefulness. In addition, nucleophilic entities such as DMAP (4-*N*,*N*-dimethylpyridine)[17,18] and P(*n*Bu)$_3$ are often used to accelerate the acyl transfer.[19] However, their use is in contrast with Anastas's Principles of Green Chemistry[20] because of the exceptionally high toxicity of the former (lethal dosage, $LD_{50} = 56\ mg\ kg^{-1}$)[21] and the high flammability of the latter (flash point = 37 °C).[22] Alternatively, the hydrohalic acid released upon formation of the ester (or amide) bond is frequently trapped with aminic bases (e.g., pyridine or triethylamine).[1] However, this procedure suffers from several chemoselectivity issues, such as the possible intramolecular migration of the acyl group if different hydroxyl functions are simultaneously present[23] or the discrimination between those alcoholic functions.[24] Interestingly, the use of an amine to facilitate an acylation is severely limited when the acid halide bears acidic α-hydrogens because of the concomitant formation of the corresponding ketene (Scheme 1, compound **C**).[25] Another important general limitation of this type of esterification reac-

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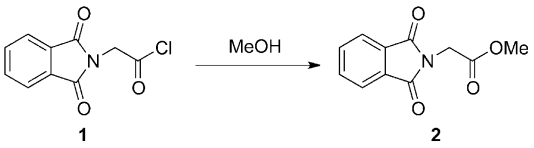
tion is rapid catalyst deactivation by deposition of char or coke on its surface, which is undesired.[16]

In this sense, the development of a simple acylation protocol for both alcohols and amines in the absence of any activator (base, acid, or catalyst) is highly desirable. For this purpose, performing reactions on the surface of solids instead of using solutions or gas phases could be a solution.[26–27] Among the inherent advantages of this strategy, we must remark on the easy isolation of products, the possibility of using mild reaction conditions (compatible with other labile groups, which could be present in the substrate), the high chemo- and regioselectivity, and the high yields obtained with almost complete suppression of by-products. Hence, the use of metal oxides has been reported; in fact, Yadav and co-workers evaluated the use of basic KF–Al_2O_3[28] and Al_2O_3 for promoting these reactions, mainly in the presence of nonphenolic systems.[29]

Herein, we present an effective approach to promote these acylation reactions, inspired by the precedents mentioned above and by our previous studies on the preparation of α-diazocarbonyl compounds from acyl halides and diazomethane, in the presence of CaO as an excellent hydrohalic acid scavenger, which allows the use of only a stoichiometric amount of the dangerous CH_2N_2.[30]

Results and Discussion

Commercially available 2-phthalimidoacetyl chloride (**1**, Scheme 2) bearing two acidic α-hydrogens (susceptible to abstraction and thus, ketene formation) was selected as the model substrate for the acylation of methanol.



1 2

Scheme 2. Model acylation of methanol with acid chloride **1**.

As shown in Table 1, formation of ester **2** is clearly improved by the presence of an acid scavenger. Interestingly, CaO was the most effective compared to other alkaline-earth metal oxide such as MgO (entry 12) or to different bases such as K_2CO_3, KF-Celite, or triethylamine (entries 13–15). The presence of 2.0 eq. CaO provided the best result, and the optimal reaction was achieved at room temperature (rt, entries 5–6). The solvent effect was prominent; initial optimization experiments were performed in diethyl ether (analogous to our previous findings regarding CaO-mediated α-diazocarbonyl preparation).[30] Evidently, an organic process performed in a toxic solvent, Et_2O, does not meet the strict safety requirements of pharmaceutical industry applications and the search for alternative, non-contaminating solvents is of great importance.[31] Therefore, in recent years we[32–35] and others[36–40] have demonstrated the beneficial effect of replacing ether-type solvents with biomass-derived (corncobs or bagasse) solvents such as 2-methyltetrahydrofuran (2-MeTHF).[41] We observed a significant improvement when switching from Et_2O to 2-MeTHF; maximizing the reaction yield to 97% (entry 6). Other solvents such as dichloromethane, *tert*-butylmethyl ether, acetonitrile, toluene, or THF, did not match the performance of 2-MeTHF (entries 7–11). Preliminary studies on analogous O-acylation reactions in the presence of catalytic CaO resulted in large amounts of carboxylic acid (originating from the hydrolysis of the acyl halide) under solvent-free conditions; this suggested the demand for a solvent in this type of reaction.[42]

Table 1. Optimization of the acylation of methanol with **2**.[a]

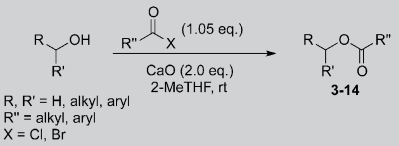
Entry	Acid scavenger	Eq.	Solvent	*T* [°C]	Reaction time [h]	Yield of **2** [%][b]
1	CaO	1.1	Et_2O	0	12	61
2	CaO	2.0	Et_2O	0	10	70
3	CaO	0.5	Et_2O	0	16	52
4	–	–	Et_2O	0	24	39
5	CaO	2.0	Et_2O	rt	8	82
6	CaO	2.0	2-MeTHF	rt	6	97(91)[c,d]
7	CaO	2.0	CH_2Cl_2	rt	10	65
8	CaO	2.0	TBME	rt	12	77
9	CaO	2.0	CH_3CN	rt	8	81
10	CaO	2.0	toluene	rt	8	72
11	CaO	2.0	THF	rt	8	85
12	MgO	2.0	2-MeTHF	rt	10	74
13	K_2CO_3	2.0	2-MeTHF	rt	8	57
14	KF-Celite	2.0	2-MeTHF	rt	8	62
15	NEt_3	2.0	2-MeTHF	rt	8	73

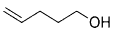
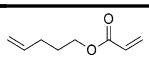
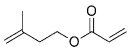
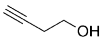
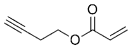
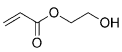
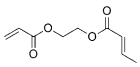
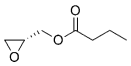
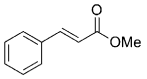
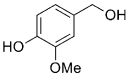
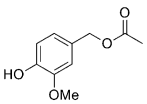
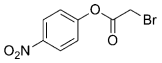
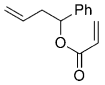
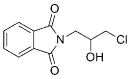
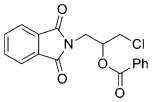
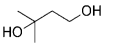
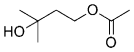
[a] Reaction conditions: acyl halide (1.05 eq.) and alcohol (1.00 eq.). [b] ^1H NMR calculated yields. [c] Isolated yield. [d] 88% isolated yield on the 0.1 mol scale.

Using the optimized conditions (CaO, rt, and 2-MeTHF), an ecofriendly process was designed; the innocuous CaO was withdrawn by using suction and the excess acyl halide (0.05 eq.) was removed through alkaline ($NaHCO_3$) washing. Interestingly, because of the low mutagenicity of 2-MeTHF[43] and its immiscibility with water,[44] the separation of the organic phase did not require any addition of noxious or environmental contaminating organic solvents (e.g., ethyl acetate, diethyl ether, hydrocarbons, or halogenated solvents), thus rendering the experimental procedure extremely simple. Importantly, the optimized reaction did not require chromatographic purification of the product; a big advancement towards the concept of ideal synthesis.

We next evaluated the substrate scope, as shown in Table 2. A series of different alcohols were efficiently acylated with different acyl halides. Aliphatic primary alcohols reacted smoothly, affording the desired esters in excellent yields; the protocol allows the incorporation of acid-sensitive functionalities such as double or triple C–C bonds, chiral epoxides, halogens, aromatic ethers, or esters. A wide range of acyl halides may be used, including highly electrophilic acryloyl-type moieties (entries 1–4, 7, 10) or sterically hindered pivaloyl chloride (entry 6). *p*-Nitrophenol reacted slower compared to aliphatic alcohols, in agreement with its lower nucleophilicity; however, this reaction did reach completion after prolonged reaction times (entry 9, 12 h). The different reactivities that were obtained as

Table 2. CaO-mediated acylation of different alcohols in 2-MeTHF.[a]



Entry	Alcohol	Acylating reagent	Reaction time [h]	Product		Yield [%][b]
1		acryloyl chloride	6		**3**	96
2		acryloyl chloride	6		**4**	90
3		acryloyl chloride	6		**5**	86
4		(*E*)-crotonyl chloride	6		**6**	94
5		butyryl chloride	6		**7**	89
6	EtOH	pivaloyl chloride	9		**8**	82
7	MeOH	cinnamoyl chloride	6		**9**	95
8		acetyl chloride	6		**10**	91
9	*p*-$NO_2C_6H_4OH$	bromoacetyl bromide	12		**11**	95
10		acryloyl chloride	9		**12**	89
11		benzoyl chloride	9		**13**	94
12		acetyl chloride	6		**14**	96

[a] Reaction conditions: acyl halide (1.05 equiv); alcohol (1.00 equiv), rt. [b] Isolated yield.

a consequence of the diverse nucleophilicity of aliphatic and aromatic alcohols were advantageously exploited for the chemoselective acylation of an aliphatic alcohol in the presence of an aromatic amine. As indicated by the crude ^{1}H NMR spectrum of the acetylation of 4-(hydroxymethyl)-2-methoxyphenol (entry 8), no modification occurred at the phenolic OH-group under the classical reaction conditions (AcCl, 1.0 eq., 6 h, rt).

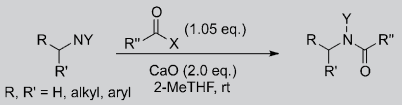
The procedure was also applied to secondary alcohols, affording the desired esters in high yields after slightly longer reaction times (entry 10, 9 h). Notably, tertiary alcohols were completely inert under the reaction conditions. Again, this fact was exploited in the chemoselective acylation of 2-methyl-2,4-butanediol (entry 12), which led to exclusive acylation at the primary alcohol site and afforded ester **14** in a 96% yield.

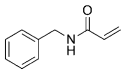
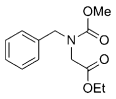
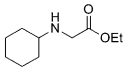
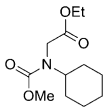
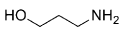
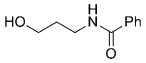
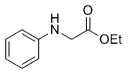
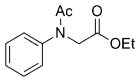
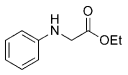
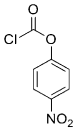
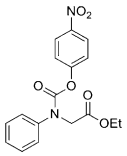
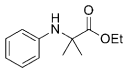
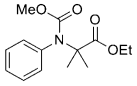
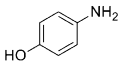
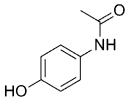
Based on these results, with the aim to develop a widely applicable acylation strategy, we focused on the acylation of amines (Table 3). This reaction is usually performed with acid anhydrides as the acylating agents; however, the use of anhydrides leads to a higher generation of waste (i.e., the other half of the molecule); therefore, the use of acyl halides would be beneficial.

The treatment of different aliphatic amines cleanly afforded the desired amides or carbamates in high yields both in the case of primary and secondary aminic functionalities. Importantly, the chemoselective benzoylation of 3-aminopropan-1-ol (entry 4) demonstrated functionalization exclusively on the nitrogen atom leaving the primary hydroxyl group unaltered, in agreement with higher nucleophilicity of an amine compared to an alcohol. Analogously, an aminophenol (entry 9) underwent acylation exclusively at the aminic site. Aromatic amines were also effective substrates for this CaO-mediated transformation, which resulted in the desired acylated products in excellent yields after only slightly increased reaction times, as a consequence of their low nucleophilicity compared to aliphatic ones. Remarkably, steric congestion in the vicinal position of nitrogen (entry 7) did not impede an efficient carbamoylation.

To study the stereochemical influence of the process, we subjected a series of optically active acyl chlorides to our stan-

Table 3. CaO-mediated acylation of different amines in 2-MeTHF.[a]



Entry	Amine	Acylating reagent	Reaction time [h]	Product		Yield [%][b]
1	$BnNH_2$	acryloyl chloride	3		**15**	95
2		methyl chloroformate	6		**16**	91
3		methyl chloroformate	5		**17**	97
4		benzoyl chloride	3		**18**	88
5		acetyl chloride	4		**19**	93[c]
6			6		**20**	82
7		methyl chloroformate	6		**21**	87
8	$PhNH_2$	acetyl chloride	4		**22**	96
9		acetyl chloride	4		**23**	93

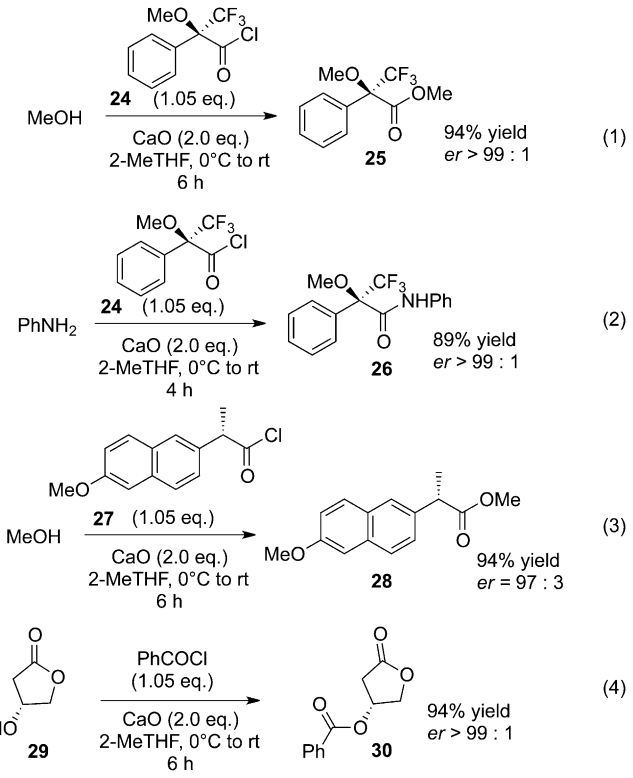
[a] Reaction conditions: acyl halide (1.05 eq.) and alcohol (1.00 eq.), rt. [b] Isolated yield. [c] 92% isolated yield on the 0.1 mol scale.

dard reaction conditions. Excellent enantioselectivities were observed both in the case of esterification and amidation of (*R*)-Mosher acid chloride **24** (Scheme 3, paths 1 and 2). Remarkably, the pharmaceutically relevant (*S*)-naproxene chloride **27**, which bears an α-acidic proton susceptible to base-mediated abstraction, also afforded the desired methyl ester **28** with an excellent enantiomeric ratio (97:3 e.r.; Scheme 3, path 3). This result confirmed that CaO does not act as a base, it is exclusively an acid trapping agent. Finally, no loss of optical purity was observed in the acylation of enantiopure alcohol **29** (Scheme 3, path 4).

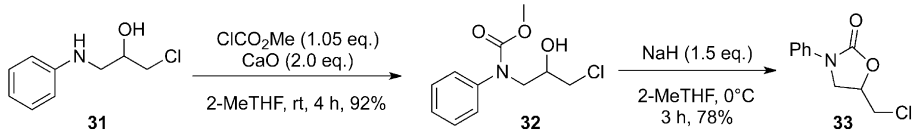
The high chemoselectivity of this protocol can be exploited for the preparation of interesting synthetic scaffolds, such as ozazolidin-2-one **33** (Scheme 4). The selective acylation of the secondary aminic function of chloroalcohol **31** with methyl chloroformate allowed the preparation of carbamate **32** in an excellent 92% yield. In a previous study we were able to obtain carbamate **32** by using a procedure that was not optimal and involved the use of a large excess of methyl chloroformate, which acylated both the alcohol and the amine at the same time. This reaction afforded the bis-protected aminoalcohol, which was hydrolyzed to the mono N-protected aminoalcohol by using aqueous methanolic potassium carbonate.[45] Herein, an improvement in obtaining compound **32** is demonstrated, which upon treatment with NaH in 2-MeTHF produced the N-aryloxazolidin-2-one **33** in a very good isolated yield (78%). N-aryloxazolidin-2-one represents the core of linezolid-type drugs.[46,47] Interestingly, the choice of base (NaH) for the second step was crucial to avoid possible concomitant epoxide ring formation.[48]

Conclusions

We demonstrate a new, efficient, chemoselective, and sustainable protocol for the stoichiometric acylation of alcohols and amines by use of CaO as an innocuous acid scavenger.



Scheme 3. Acylation of alcohols and amines with enantiopure acyl chlorides (paths 1–3) and the acylation of an enantiopure alcohol (path 4).



Scheme 4. Chemoselective protection of a secondary amine in the presence of a secondary alcohol during the preparation of an N-aryloxazolidin-2-one.

No competitive ketene formation is observed for acylating agents bearing acidic α-hydrogens. Furthermore, the procedure allows the acylation of primary alcohols in a chemoselective manner in the presence of phenols or tertiary alcohols. The proposed technique can also be used to acylate amines in the presence of alcohol functionalities. The use of 2-MeTHF as the solvent is crucial and it leads to maximized yields; it can also prevent the need for chromatographic purifications.

Experimental Section

Synthesis of ester 2

To a solution of methanol (400 mg, 12.5 mmol, 1.0 eq.) in 2-MeTHF (25 mL), CaO (1.40 g, 25.0 mmol, 2.0 eq., dried over night over P_2O_5 in a desiccator) was added and the resulting suspension was stirred at rt for 5 min. Afterwards, a solution of phthaloyl chloride (2.93 g, 13.1 mmol, 1.05 eq.) in 2-MeTHF (10 mL) was added dropwise over 5 min. The mixture was stirred for 6 h and subsequently filtered in vacuo before washing with 2-MeTHF (20 mL). The solution was washed with aqueous saturated $NaHCO_3$ (10 mL) and the two resulting phases were separated; the organic phase (2-MeTHF) was dried over anhydrous $MgSO_4$, filtered, and dried in vacuo to give **2** as a colorless solid (mp 113 °C) in 96% yield (2.63 g), which did not require further purification. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.79$ (dd, $J = 5.5$, 3.1 Hz, 2H, CH-Ar), 7.66 (dd, $J = 5.5$, 3.1 Hz, 2H, CH-Ar), 4.36 (s, 2H, CH_2), 3.68 ppm (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): $\delta = 167.6$ (CO), 167.3 (CO), 134.2 (CH), 131.9 (C), 123.5 (CH), 52.6 (CH_2), 38.6 ppm (CH_3); IR (KBr): $\tilde{\nu} = 1731$, 1694, 1595, 1208, 909 cm^{-1}; elemental analysis (%) for $C_{11}H_9NO_4$: calculated: C, 60.27; H, 4.14; N, 6.39, and measured: C, 60.51; H, 4.01; N, 6.19.

Synthesis of amide 23

To a solution of 4-aminophenol (400 mg, 3.7 mmol, 1.0 eq.) in 2-MeTHF (9 mL), CaO (415 mg, 7.4 mmol, 2.0 eq., dried over night over P_2O_5 in a desiccator) was added and the resulting suspension was stirred at rt for 5 min. Afterwards, a solution of acetyl chloride (306 mg, 3.9 mmol, 1.05 eq.) in 2-MeTHF (4 mL) was added dropwise over 5 min. The mixture was stirred for 4 h and subsequently filtered in vacuo and washed with 2-MeTHF (12 mL). The solution was washed with aqueous saturated $NaHCO_3$ (8 mL) and the two resulting phases were separated; the organic phase (2-MeTHF) was dried over anhydrous MgSO4, filtered, and dried in vacuo to give **23** as a colorless solid (mp 170 °C) in 93% yield (548 mg). ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): $\delta = 9.65$ (s, 1H, NH), 9.13 (s, 1H, OH), 7.34 (d, $J = 8.8$ Hz, 2H, CH-Ar), 6.68 (d, $J = 8.8$ Hz, 2H, CH-Ar), 1.98 ppm (s, 3H, CH_3); ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C): $\delta = 167.5$ (CO), 153.1 (C), 131.0 (C), 120.8 (CH), 115.0 (CH), 23.7 ppm (CH_3); IR (KBr): $\tilde{\nu} = 3430$, 1662, 1591 cm^{-1}; elemental analysis (%) for $C_8H_9NO_2$: calculated: C, 63.56; H, 6.00; N, 9.27, and measured: C, 63.70; H, 6.13; N, 9.12.

(See the Supporting Information for full experimental procedures, compound characterization, and copies of ^{1}H and ^{13}C NMR spectra).

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Keywords: acylation · alcohols · amines · chemoselectivity · solvent effects

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