Synlett J.-M. Vatèle Letter

TEMPO-Catalyzed Oxidative Amidation of Alcohols via Hexafluoroisopropyl Esters

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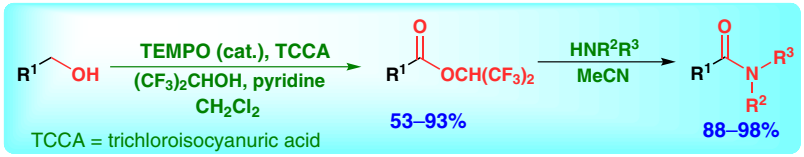

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Abstract Stepwise oxidative amidation of alcohols using trichloroisocyanuric acid, a catalytic amount of TEMPO in combination with pyridine and hexafluoroisopropyl (HFIP) alcohol followed by amines is described. This procedure used HFIP esters as activating esters which were found to be very efficient acylating agents for amide bond formation. This process is compatible with a number of functional groups and acid-sensitive protecting groups.

Key words alcohols, amidation, hexafluoroisopropyl esters, tandem oxidative process, TEMPO

The amide bond is one of the most important linkages in organic synthesis and constitutes the key motif in peptides, natural products, agrochemicals, pharmaceuticals and polymers.[1] It is estimated that more than 25% of known drugs contain an amide functional group.[2] The conventional approach for the synthesis of amides is the coupling of activated carboxylic acid derivatives with amines.[3] However, these methods have the drawbacks of generating a stoichiometric amount of by-products and employing hazardous reagents. An attractive alternative redox approach to amide formation is acylation of amines from aldehydes or even better alcohols.[4] Indeed, the direct amidation of alcohols with amines through aldehydes is a potentially elegant alternative pathway since it uses cheap, abundant and stable materials. Milstein and co-workers were the first to report a direct amidation of alcohols using a dehydrogenative pathway with a ruthenium pincer complex.[5] Other metal-catalyzed oxidation of alcohols to amides were further described.[6] Amidation via *N*-hydroxysuccinimide esters was reported using IBX[7a] or TBHP in the presence of NBu_4I[7b] as oxidants. Although these systems provide a new route to amides, they suffer from drawbacks such as narrow substrate scope,[6,7a] hydrogenation of unsaturated compounds[5] or low yields.[7a]

In continuation of our interest in the development of novel synthetic applications of TEMPO/co-oxidants systems,[8] we envisaged that amides could be synthesized from alcohols by a TEMPO-catalyzed tandem oxidation process (TOP)[9] through an active ester. In 2012, Barbas and co-workers developed a tetrabutylammonium iodide catalyzed amidation and esterification of aldehydes with activating agents by a cross-coupling strategy.[10] Among the active intermediates studied, we focused our attention to hexafluoroisopropyl (HFIP) esters. These active esters were only used sparingly in organic synthesis as acylating agents particularly in the synthesis of peptides,[11] amides,[12] and in lactamization[13] and transesterification[14] reactions. A major advantage of HFIP esters compared to other active esters is that hexafluoroisopropanol formed during the substitution reaction is easy to remove by simple evaporation because of its low boiling point (58 °C). In 2004, Bobbitt and co-workers reported the first example of oxidative dimerization of alcohols to esters using a large excess of an oxoammonium salt in the presence of pyridine, a crucial reagent for the oxidation to take place.[15,16] Later on, Szpilman and co-workers showed that this oxidation could work as well by using a catalytic amount of TEMPO and a terminal oxidant.[17] They also reported a new method of mixed anhydride synthesis from aldehydes and pivalic acid with a TEMPO/*t*-BuOCl/pyridine system and these mixed anhydrides were further transformed to esters and amides via a one-pot procedure.[18] In 2013, Leadbeater and co-workers reported the oxidative esterification of aldehydes to HFIP esters using the Bobbitt oxidation procedure.[19] They also highlighted that an interesting feature of HFIP esters is that, in contrast to most esters, they can be readily transformed to alcohols, acids and other esters under mild conditions. However, a draw-

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back to this method is the use of a large excess of the relatively expensive 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate and pyridine as solvent.

Table 1 Scope of the HFIP Ester Formation from Alcohols

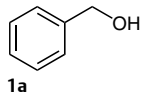
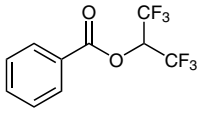
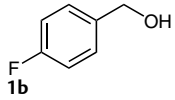
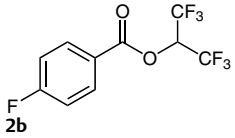
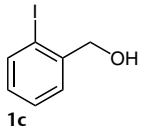
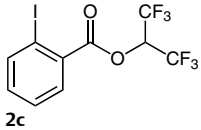
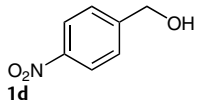
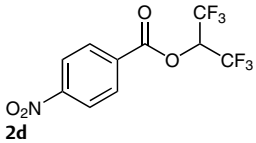
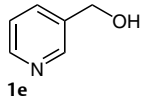
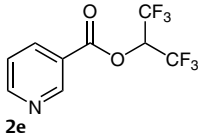
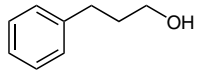
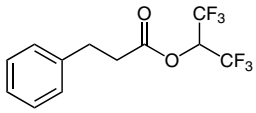
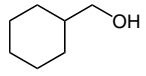
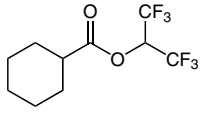
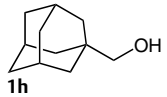
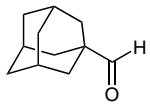
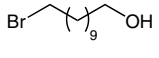
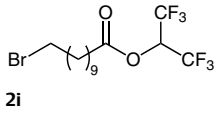
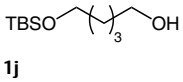
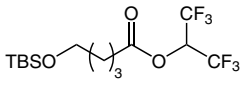
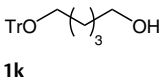
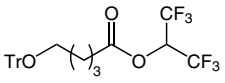
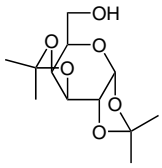
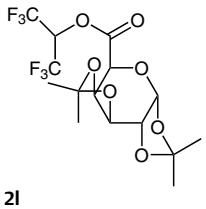
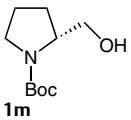
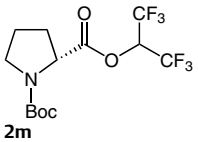
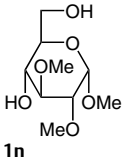
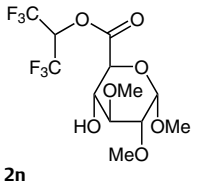
Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	 **1a**	10	 **2a**	85
2	 **1b**	10	 **2b**	89
3	 **1c**	10	 **2c**	75
4	 **1d**	10	 **2d**	93
5	 **1e**	8	 **2e**	87
6	 **1f**	0.5	 **2f**	82
7	 **1g**	2	 **2g**	65[b]
8	 **1h**	24	 **2h**	81
9	 **1i**	1	 **2i**	84

Table 1 (continued)

Entry	Substrate	Time (h)	Product	Yield (%)[a]
10	 **1j**	1.5	 **2j**	79[b,c]
11	 **1k**	1.5	 **2k**	81[b,c]
12	 **1l**	1.5	 **2l**	88[b,c]
13	 **1m**	1.5	 **2m**	59[b,c,d]
14	 **1n**	2	 **2n**	53[b,c,d]

[a] Isolated yield.
[b] $NaHCO_3$ (8 equiv) was added.
[c] Reaction was run at 0 °C.
[d] Some decomposition occurred.

For our studies we chose trichloroisocyanuric acid (TCCA) as terminal oxidant for TEMPO-catalyzed oxidative esterification of alcohols because it is a very cheap and non-toxic reagent and has been used with success in a number of TEMPO-catalyzed oxidation reactions.[17,20] After some experimentation on the model substrate **1f**, the HFIP ester **2f** could be obtained in 82% yield by treatment of the alcohol **1f** in CH_2Cl_2[21] with TEMPO (5 mol%) and TCCA (1.2 equiv) added by portions at 0 °C followed, after consumption of the alcohol, by HFIP alcohol (2 equiv) and pyridine (4 equiv) and stirring the suspension for 30 minutes at room temperature (Table 1, entry 6). The resulting ester was easily purified by filtration of the suspension through a pad of silica gel. Under the optimized reaction conditions, we examined the general applicability of the oxidative esterification for a range of structurally diverse primary alcohols (Table 1).[22,23] Good to excellent yields were obtained in most cases. Both electron-rich and electron-poor benzyl al-

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cohols and the heteroaromatic compound **1e** reacted at about the same rate but much slower than aliphatic alcohols (Table 1, entries 1–5). The oxidative esterification of aldehydes was the rate-determining step for these aromatic substrates. Allylic alcohols such as geraniol and cinnamyl alcohol gave mainly chlorinated products at the aldehyde formation stage in contrast to what was reported by Giacomelli and co-workers.[20a]

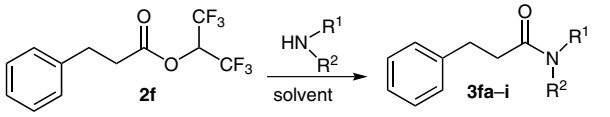
Next, we turned our attention to the study of the oxidation of a range of aliphatic alcohols. Under the standard conditions, cyclohexylmethanol **1g** gave mainly aldol products. In contrast, when the reaction was carried out in the presence of an excess of $NaHCO_3$, the desired ester **2g** was obtained in 65% yield (Table 1, entry 7).[24] In the presence of this additive, substrates **1j**–**1m** containing acid-sensitive protecting groups such as trityl, TBS, isopropylidene and Boc afforded the corresponding esters in moderate to excellent yields (Table 1, entries 10–13). In the case of sterically hindered 1-adamantane methanol **1h**, only the corresponding aldehyde **2h** was isolated, with no ester formation being observed (Table 1, entry 8). Ester **2n** was obtained in only a moderate yield from the substrate **1n**, bearing a secondary alcohol, because some degradation occurred during the addition of HFIP alcohol and pyridine (Table 1, entry 14).

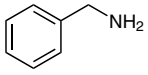
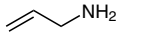
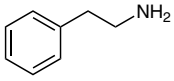
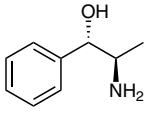
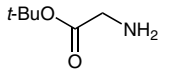
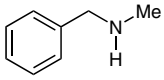
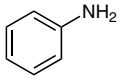
We next studied the scope of amide formation on the ester **2f** with a range of primary and secondary amines (Table 2). Amidation of **2f** with primary amines occurred readily in CH_2Cl_2 and in excellent yields (Table 2, entries 1–3).

Sterically hindered norephedrin reacted more slowly to give the amide **3fd** in 53% yield after 30 hours (Table 2, entry 5). The rate and yield were improved by using acetonitrile in place of dichloromethane (Table 2, entry 4). Nucleophilic substitution with glycine *tert*-butyl ester provided the *N*-acyl amino acid **3fe** in quantitative yield (Table 2, entry 6). Among the secondary amines tested, pyrrolidine reacted readily with **2f** at room temperature to afford **3fg** in 97% yield (Table 2, entry 8). With poor nucleophiles such as aniline and *N*,*O*-dimethylhydroxylamine, no amide formation was observed even in refluxing acetonitrile for 24 hours (Table 2, entries 9 and 10). The relative reactivity of amines toward HFIP ester **2f** is in good agreement with that reported with *N*-hydroxysuccimide esters by Hanna and Cline and is correlated, for the majority of amines, with their basicity.[25]

We then turned our attention to the amidation of HFIP esters **2a**–**n** with a range of amines (Table 3).[26] In all cases, amides were obtained in excellent yields (81–98%). We first studied the reactivity of diversely substituted aromatic esters with benzylamine (Table 3, entries 1–5). Compound **2d** bearing an electron-withdrawing group and the pyridine derivative **2e** underwent amidation more rapidly than those having electron-donating groups (Table 3, entries 2–5). The nucleophilic substitution of HFIP esters is sensitive

Table 2 Scope of the Aminolysis of the HFIP Ester **2f** with Primary and Secondary Amines



Entry	Amine	Solvent	Time (h)	Temperature	Product	Yield (%)[a]
1		CH_2Cl_2	12	r.t.	**3fa**	98
2		CH_2Cl_2	5	r.t.	**3fb**	95
3		CH_2Cl_2	10	r.t.	**3fc**	99
4		MeCN	30	r.t.	**3fd**	90
5		CH_2Cl_2	30	r.t.		53[b]
6		MeCN	3	reflux	**3fe**	97
7		MeCN	9	reflux	**3ff**	96
8		MeCN	1	r.t.	**3fg**	97
9		MeCN	24	reflux	**3fh**	0
10		MeCN	24	reflux	**3fi**	0

[a] Isolated yield.
[b] About 38% of the starting material was recovered.

to steric hindrance as illustrated by the slow addition of phenethylamine to ester **2g** (Table 3, entry 6). Amidation of substrate **2i** with benzylamine, bearing a bromo group, a potential leaving group, gave the desired amide **3i** in a good yield with no observable other products (Table 3, entry 7). Amidation of a number of functionalized aliphatic esters occurred smoothly to yield the corresponding amides in excellent yields (Table 3, entries 8–12). It is noteworthy that the specific rotation of *N*-Boc proline *N*-benzylamine **3m** is identical to that reported in the literature showing that all steps from *N*-Boc prolinol **1m** occurred without any racemization (Table 3, entry 11).[27,28]

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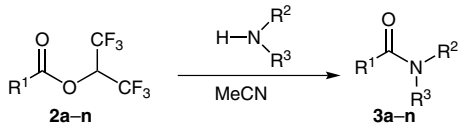
Table 3 Amide Formation from HFIP Esters



2a–n **3a–n**

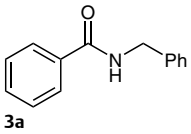
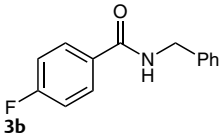
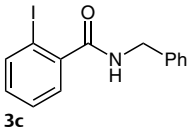
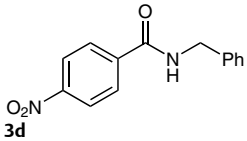
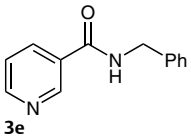
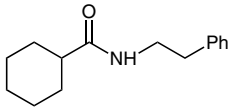
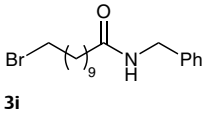
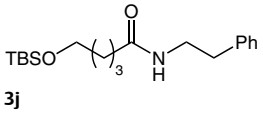
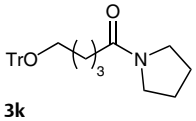
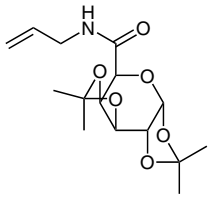
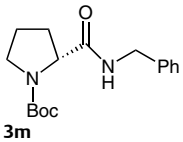
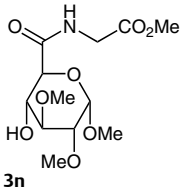
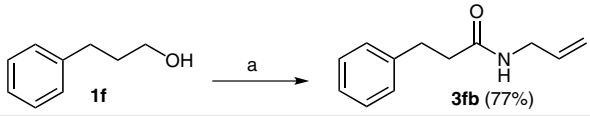
Entry	Substrate	Time (h)	Amide	Yield (%)[a]
1	**2a**	9	 **3a**	97
2	**2b**	9	 **3b**	95
3	**2c**	12	 **3c**	98
4	**2d**	1	 **3d**	96
5	**2e**	2	 **3e**	95
6	**2g**	4[b]	 **3g**	98
7	**2i**	7	 **3i**	81
8	**2j**	5	 **3j**	97
9	**2k**	1	 **3k**	97

Table 3 (continued)

Entry	Substrate	Time (h)	Amide	Yield (%)[a]
10	**2l**	1	 **3l**	96
11	**2m**	5	 **3m**	96
12	**2n**	2	 **3n**	88

[a] Isolated yield.
[b] The reaction was carried out at reflux.

To illustrate the utility of our alcohol oxidative amidation process, we conducted the amidation of 3-phenylpropanol (**1f**) by a one-pot procedure and the *N*-allyl amide **3fb** was obtained in 77% yield after purification on a column of silica gel (Scheme 1).



1f **3fb** (77%)

Scheme 1 *Reagents and conditions*: (a) TEMPO (5 mol%), $NaHCO_3$ (8 equiv), TCCA (1.2 equiv), CH_2Cl_2, 0 °C, 30 min then HFIP alcohol (2 equiv), pyridine (4 equiv), r.t., 30 min, then allylamine (6 equiv), r.t., 6 h.

In summary, we have disclosed a methodology for amidation of alcohols under mild conditions via a TEMPO-mediated oxidative esterification of alcohols to HFIP esters and N-acylation with primary and secondary amines. A large number of diversely functionalized amides were synthesized by this three-step sequence in good yields generating, in the last step, the volatile HFIP alcohol as a by-product. Finally, the feasibility of a one-pot procedure for this oxidative amidation of alcohols has been demonstrated.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1381056.

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(21) In MeCN, several products were formed at the aldehyde formation stage.

(22) Appropriate physical and analytical data were obtained for all new compounds (see Supporting Information).

(23) **TEMPO-Oxidative Esterification of Alcohols with HFIP Alcohol; General Procedure**: To a cooled (0 °C) solution of the alcohol (1 mmol) in CH_2Cl_2 (2 mL) were added successively TEMPO (7.8 mg, 5 mol%), TCCA (278 mg, 1.2 equiv) in portions and the suspension was stirred until the consumption of the alcohol (progress of the reaction was monitored by TLC). In the case of substrates **2g,j**–**n**, $NaHCO_3$ (8 equiv) was added before the addition of TCCA. HFIP alcohol (210 µL, 2 equiv) and pyridine (320 µL, 4 equiv) were then successively added dropwise at 0 °C. After warming, the solution was stirred at r.t. until consumption of the aldehyde (for substrates **1j**–**n**, the oxidative esterification was conducted at 0 °C). The yellow suspension was poured onto a small column of silica gel and the HFIP ester was eluted with petroleum ether or a mixture of petroleum ether–Et_2O.
1,1,1,3,3,3-Hexafluoropropan-2-yl-5-[(*tert*-butyldimethylsilyl)oxy]pentanoate (2j): Eluent: PE–Et_2O (97:3); yield: 79%; liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.77 (hept, *J* = 6.2 Hz, 1 H), 3.63 (t, *J* = 6.1 Hz, 2 H), 2.55 (t, *J* = 7.4 Hz, 2 H), 1.68–1.93 (m, 2 H), 1.56 (dq, *J* = 9.9, 6.2 Hz, 2 H), 0.88 (s, 9 H), 0.04 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 120.5 (q, *J* = 282 Hz), 66.3 (sept, *J* = 35 Hz), 62.3, 33.0, 31.7, 25.8 (3 × C), 21.3, 18.3, –5.5 (2 × C).^{19}F NMR (283 MHz): δ = –73.39 (d, *J* = 6.1 Hz). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{24}F_6NaO_3Si$: 405.1291; found: 405.1292.

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(26) **Amide Formation from HFIP Esters; General Procedure**: To a solution of HFIP ester (1 mmol) in MeCN (2 mL) was added the amine (2 equiv except for allylamine: 3 equiv) and the solution was stirred at r.t. (at reflux for entries 6 and 7 in Table 2 and entry 6 in Table 3) for the reaction time indicated in Tables 2 and 3. The solution was concentrated and the amide was separated from the excess of amine on a pad of silica gel using a mixture of petroleum ether–EtOAc as eluent.
5-[(*tert*-Butyldimethylsilyl)oxy]-*N*-phenethylpentanamide (3j): Eluent: PE–EtOAc (2:1); yield: 97%; oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 6.92–7.32 (m, 5 H), 5.58 (br s, 1 H), 3.52 (t, *J* = 6.3 Hz, 2 H), 3.41–3.45 (m, 2 H), 2.65 (t, *J* = 7.1 Hz, 2 H), 1.93 (t, *J* = 7.2 Hz, 2 H), 1.64–1.78 (m, 2 H), 1.44–1.57 (m, 2 H), 0.98 (s, 9 H), 0.006 (s, 6 H). ^{13}C NMR (75 MHz, C_6D_6): δ = 172.3, 139.7, 129.1 (2 × C), 128.8 (2 × C), 126.6, 63.1, 41.0, 36.3, 36.2, 32.8, 26.2 (3 × C), 22.6, 18.5, –5.1 (2 × C). HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{34}NO_2Si$: 336.2353; found: 336.2344.
For other compounds, see Supporting Information.

(27) $[\alpha]_D^{20}$ +81.5 (*c* 1, $CHCl_3$) for compound **3m** {see ref. 28 for the (*S*)-enantiomer $[\alpha]_D^{20}$ –80.8 (*c* 1, CH_2Cl_2)}.

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