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A convenient and simple procedure for the preparation of nitrate esters from alcohols employing $LiNO_3/(CF_3CO)_2O$

Adina Gavrila, Lisbeth Andersen and Troels Skrydstrup*

Department of Chemistry, University of Aarhus, Langelandsgade 140, 8000 Aarhus C, Denmark

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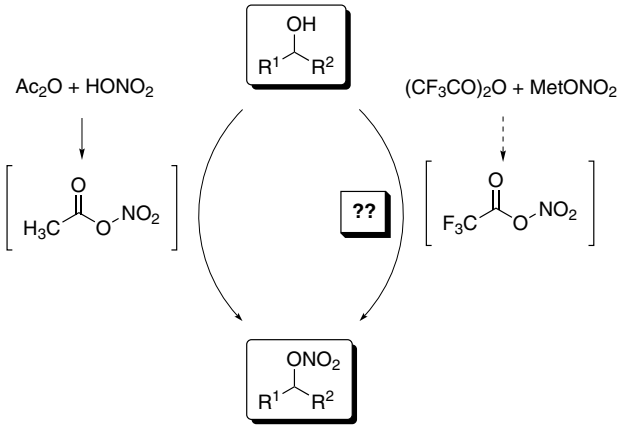
Abstract—Alcohols in small peptides, monosaccharides and steroids (12 examples) are conveniently transformed to their corresponding nitrate esters upon treatment with an acetonitrile solution of $LiNO_3$ and trifluoroacetic anhydride. The in situ formed mixed anhydride (CF_3COONO_2) is proposed to be the reactive nitration reagent.

Subjection of nitrate esters to either photolysis or tributyltin hydride–AIBN represents a viable source of alkoxy radicals. Depending on the substrates, such reactive radicals have successfully been exploited for synthetically useful fragmentations,[1–8] as well as hydrogen atom abstractions.[9] For example, Easton and co-workers have demonstrated that nitrate esters of β-hydroxy-α-amino acid derivatives react with tributyltin hydride to afford alkoxy radicals, which can readily undergo β-scission, providing a convenient route for the regiocontrolled production of α-carbon-centred amino acid radicals.[10,11]

Our interest in the generation of glycyl radicals via the samarium diiodide promoted reduction of functionalized peptides[12–14] prompted us to examine the use of such nitrate esters of β-hydroxy-α-amino acid derivatives. However, concerned about the compatibility and reproducibility of the conditions for known nitration reactions of alcohols (fuming nitric acid,[15–17] mixtures of nitric and sulfuric acid,[15,17] boron trifluoride hydrate–potassium nitrate[18]), we set out to develop a more convenient one-step synthesis of nitrate esters from alcohols.[19] In this report, we demonstrate that the combination of $LiNO_3/(CF_3CO)_2O/Na_2CO_3$ in acetonitrile provides a viable means for carrying out such transformations under mild conditions.

One of the more common methods for the conversion of alcohols to nitrate esters requires treatment of an alcohol with a reactive mixed anhydride (acetyl nitrate) in either acetic anhydride or acetic acid.[15–17] As this nitration species is formed in situ from fuming nitric acid and acetic anhydride, we explored the possibility of generating a more reactive mixed anhydride under less harsh conditions starting from a nitrate salt and trifluoroacetic anhydride (Scheme 1). The results of this study are depicted in Table 1 with the serine containing dipeptide **1**.

Attempts were first made by simply mixing equimolar amounts of dried lithium nitrate with trifluoroacetic anhydride in various solvents. In all cases, the two reagents were stirred together for 30 min at 20 °C and



Scheme 1.

Keywords: Nitrate esters; Alcohols; Peptides; Carbohydrates; Steroids.
* Corresponding author. Tel.: +45 8942 3932; fax: +45 8619 6199; e-mail: ts@chem.au.dk

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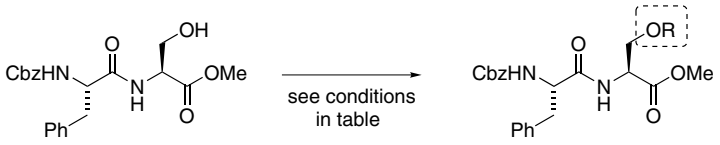
Table 1. Nitration studies with the dipeptide **1**



1

2 R = NO_2
3 R = $COCF_3$

Entry	Nitration reagent	Solvent	Temperature (°C)	Yield of nitrate ester **2**[a] (%)	Yield of trifluoroacetate **3** (%)
1	$LiNO_3$/TFAA	CH_2Cl_2	0	—	93
2	$LiNO_3$/TFAA	THF	0	—	—
3	$LiNO_3$/TFAA	CH_3CN	0	70	20
4	$LiNO_3$/TFAA Na_2CO_3	CH_3CN	0	91	3
5	$LiNO_3$/TFAA Na_2CO_3	CH_3CN	20	80	15
6	$NaNO_3$/TFAA Na_2CO_3	CH_3CN	0	—	—
7	$Mg(NO_3)_2$/TFAA Na_2CO_3	CH_3CN	0	—	—
8	$Al(NO_3)_3$/TFAA Na_2CO_3	CH_3CN	0	—	—
9	$LiNO_3$/Ac_2O	Ac_2O	0	—	—

[a] Isolated yields after recrystallization from EtOAc/pentane.

then cooled to 0 °C prior to the addition of **1** (0.5 equiv). Use of dichloromethane furnished almost exclusively the corresponding trifluoroacetate **3** after a reaction time of 5 h (entry 1), which is explained by the lack of formation of the mixed anhydride due to the insolubility of the lithium nitrate. However, in both THF and acetonitrile, a clear solution was obtained after stirring the two reagents for approx 30 min. Whereas with THF as the solvent, multiple products were formed upon addition of the dipeptide (entry 2), in acetonitrile the desired nitrate **2** could be isolated as the major product in 70% yield after recrystallization (entry 3). Nevertheless, the ^1H NMR spectrum of the crude reaction mixture revealed the presence of the trifluoroacetate **3** (entry 3) with a ratio of **2**:**3** equal to 3.5:1. Performing the same reaction in the presence of sodium carbonate in order to neutralize the trifluoroacetic acid generated during the reaction, improved the ratio of **2**:**3** considerably and provided the nitrate ester in 91% yield (entry 4).[20,21] Increasing the reaction temperature led to a decrease in the ratio (entry 5). As indicated in entries 6–8, use of other nitrate sources proved ineffective for nitrate ester formation. Likewise, treatment of the alcohol **1** with $LiNO_3$ in acetic anhydride also did not provide any yield of the nitrate ester **2** (entry 9).

With the identification of appropriate reaction conditions for the alcohol to nitrate ester transformation, we investigated the suitability of this approach to a variety of other alcohols as illustrated in Table 2.[20] As indicated, hydroxyl groups present in peptides (entries 1–5), monosaccharides (entries 6–9) and steroids (entries 10 and 11) were conveniently converted to the nitrate esters in acceptable to good yields upon subjection to the $LiNO_3$/$(CF_3CO)_2O$/Na_2CO_3 combination in acetonitrile. The derivatized peptides, carbohydrates and steroids were all purified by recrystallization as chromatography led to reduced yields of some of the nitrate esters particularly with the peptide substrates due to their ability to undergo facile β-elimination. A double nitration of the *tert*-butyl ester of deoxycholic acid was

Table 2. Formation of nitrate esters with $LiNO_3$/$(CF_3CO)_2O$/Na_2CO_3 in acetonitrile

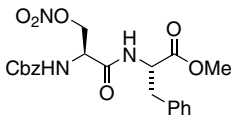
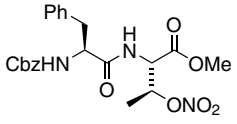
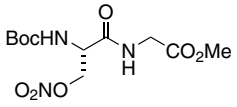
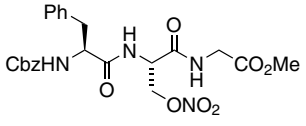
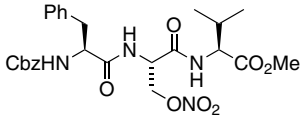
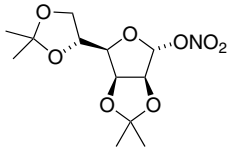
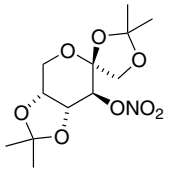
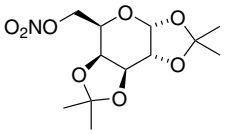
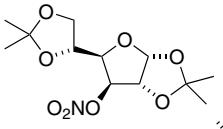
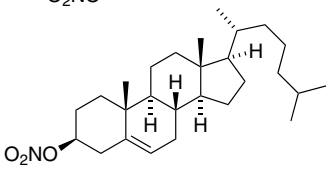
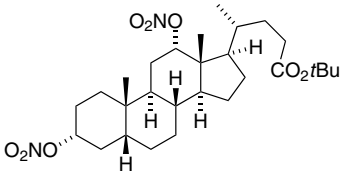
Entry	Yield of nitrate ester[a] (%)	Nitrate ester
1	70	
2	87	
3	50	
4	63	
5	80	
6	63	
7	59	

Table 2 (*continued*)

Entry	Yield of nitrate ester[a] (%)	Nitrate ester
8	89	
9	80	
10	82	
11	65[b]	

[a] Isolated yield after recrystallization.
[b] 4 equiv of the nitration reagents used.

also possible providing the corresponding dinitrate diester in 65% yield (entry 11).

In conclusion, we have developed an alternative approach for the nitration of alcohols under mild conditions via a mixed anhydride generated from $LiNO_3$/$(CF_3CO)_2O$. Further work is in progress to test the compabtibility of this approach with longer peptides, as well as cyclic peptides and to examine the ability of these nitrates to undergo reduction upon subjection to samarium diiodide. This work will be reported in due course.

Acknowledgements

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19. Other two-step procedures are also known such as alcohol to sulfonate transformation followed by substitution with a nitrate salt (Ref. 3), or generation of a chloroformate followed by treatment with silver nitrate (Ref. 18).
20. *General procedure for the nitration of alcohols*: Trifluoroacetic anhydride (2.0 mmol) was added to a solution of $LiNO_3$ (2.0 mmol) in dry acetonitrile (5 mL) at 20 °C. The mixture was stirred until complete dissolvation of $LiNO_3$ (approx 30 min) and the solution was then cooled to 0 °C. Sodium carbonate (2.0 mmol) and the alcohol (1.0 mmol) were then added and the reaction mixture was stirred for 5–7 h. The reaction mixture was poured into an ice-cold solution of saturated $NaHCO_3$. Extraction with CH_2Cl_2 followed by drying and evaporation under reduced pressure afforded the nitrate ester, which was purified by recrystallization from EtOAc/hexane. Column chromatography with the same solvent system led to reduced yields for the peptide nitrates.
21. *Data for compound* **2**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.38–7.15 (m, 10H), 6.77 (br s, 1H), 5.24 (br s, 1H), 5.10 (d, 1H, $J = 10.0$ Hz), 5.07 (d, 1H, $J = 9.0$ Hz), 4.83 (m, 1H), 4.76 (br d, 1H, $J = 11.3$ Hz), 4.69 (dd, 1H, $J = 11.3$, 3.9 Hz), 4.49 (m, 1H), 3.76 (s, 3H), 3.13 (dd, 1H, $J = 14.0$, 6.8 Hz), 3.07 (dd, 1H, $J = 13.7$, 6.6 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 171.4, 168.4, 156.2, 136.2, 136.0, 129.4, 129.2 (2C), 129.1, 129.0, 128.7, 128.5, 128.3, 127.4, 71.1, 67.5, 56.2, 53.4, 50.8, 38.2. ES-HRMS $C_{21}H_{23}N_3O_8$ [M+Na$^+$]: Calculated: 468.1383, found: 468.1391.