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Practical catalytic nitration directly with commercial nitric acid for the preparation of aliphatic nitroesters†

Jichao An, Peipei Liu, Mengyuan Si, Wenhao Li, Pan He, Bo Yang * and Guanyu Yang *

To pursue a sustainable and efficient approach for aliphatic nitroester preparation from alcohol, europium-triflate-catalyzed nitration, which directly uses commercial nitric acid, has been successfully developed. Gram scalability with operational ease showed its practicability.

Aliphatic nitroesters are a class of important organic compounds that have been used widely in modern science and technology. Since nitroglycerine was first applied as a drug in 1870, the clinical usefulness of nitroesters in treating stable angina continues to this day (for over 140 years).[1] The four most common antianginal drugs are glyceryl trinitrate (**GTN**), nicorandil, isosorbide-5-mononitrate (**ISMN**) and isosorbide-2,5-dinitrate (**ISDN**) (Fig. 1). At the same time, the unique chemistry of the nitro group has led to the use of several nitroesters in high-energy materials, such as **GTN**, pentaerythritol tetranitrate (**PETN**), sorbitol hexanitrate (**SHN**) (used as explosives/propellants),[2] and 2-ethylhexyl nitrate (**EHN**) as a cetane number improver of diesel (Fig. 1).[3]

The *O*-nitration of alcohols is the main synthetic method of nitroesters, which may be carried out using a number of electrophilic nitrating reagents, such as nitric-sulfuric acid, KNO_3/BF_3,[4] nitrogen dioxide or pentoxide,[5] $(CH_3CO)_2O/HNO_3$,[3] thionyl nitrate,[6] nitronium tetrafluoroborate[7] *etc*. It is widely recognized that the *o*-nitration of alcohols undergoes the electrophilic substitution of H of the alcohol hydroxyl group by a nitronium ion which is formed from nitrating reagents under acidic (Brønsted or Lewis acid) nitration conditions.[3] Among them, due to the obvious cost advantage, mixed-acid nitration, which involves the use of a mixture of nitric acid and excess concentrated sulfuric acid as the nitrating agent, is a traditional and currently well-used method for the production of many commercial large-volume nitroesters. However, this process produces a lot of environmentally hazardous acidic waste, and it has many other disadvantages including low selectivity, overnitration, generation of oxidized products and equipment corrosion. Therefore, the development of new environmentally friendly nitration methods for nitroester preparation is highly desirable in the chemical industry.

Undoubtedly, catalytic nitration, which involves the direct use of inexpensive commercially available concentrated HNO_3 as the nitrating reagent without concentrated sulfuric acid, seems preferable. To develop the catalytic nitration with nitric acid, solid acids,[8] lanthanide(III) triflates [$Ln(OTf)_3$, Ln = La–Lu],[9] $Bi(OTf)_3$[10], *etc.* had been used to catalyze nitrations. However, these catalytic nitrations focused on aromatic[11] and aliphatic[12] *C*-nitrations, barely exploring the *O*-nitration of alcohols. Herein, we report a new catalytic method for the one-pot *O*-nitration of alcohols to nitroesters with HNO_3 by metal triflates.

Our preliminary attempt at the catalytic *O*-nitration of alcohols explored the performance of various metal triflates. Therein, the *O*-nitration of 2-ethylhexanol to **EHN** using 1.4 equivalents of concentrated (65 wt%) HNO_3 was selected as

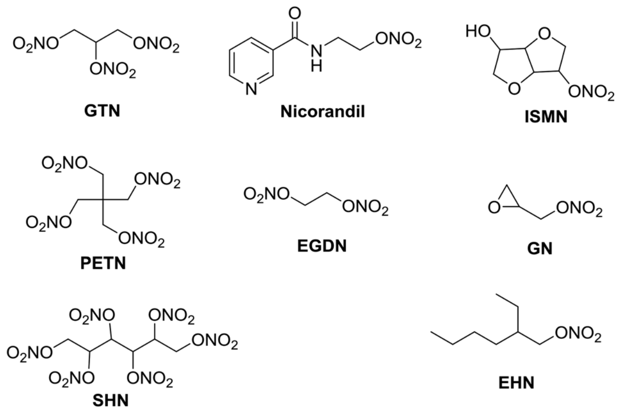

Fig. 1 Several commercial nitroesters.

College of Chemistry, Zhengzhou University, Zhengzhou, 450001, China.
E-mail: yb08220425@163.com, yangguanyu@zzu.edu.cn

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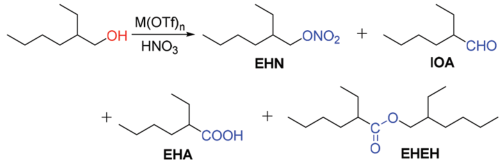
the model reaction which was conducted in 1,2-dichloroethane (DCE) at 90 °C for 5 h in the presence of 5 mol% urea (based on HNO_3) (Table 1). In contrast to the catalytic nitration of 2-ethylhexanol, $M(OTf)_n$-free reactions were conducted (entries 1 and 2, Table 1). The reaction results showed that in the absence of urea it took place in a disorderly manner to afford a product mixture of **EHN**, isooctanal (**IOA**), 2-ethylhexanoic acid (**EHA**) and 2-ethylhexyl 2-ethylhexanoate (**EHEH**), meaning that the nitration, oxidations and esterization occurred together and that the oxidations were the main reactions. When urea was employed as the stabilizer of HNO_3, the nitration afforded a single product **EHN**, and the oxidations could be avoided completely. Therefore, further tests were conducted to screen $M(OTf)_n$ with 5 mol% urea. As can be seen, in comparison with the poor performance of the alkali metal Na, the triflates of the alkaline earth metals Mg, Ca, and Ba displayed comparative catalytic activities (entries 3–6). $Bi(OTf)_3$ realized 21.2% conversion (entry 7), which was lower than the efficiencies of aryl *C*-nitrations.[10] As always, transition metals worked well, and Cu and Fe helped achieve conversions as high as 68.1% and 47.0%, respectively. However, so many sorts of by-products were formed that poor selectivities of **EHN** were achieved (entries 8 and 9). In contrast, lanthanide(III) triflates displayed better catalytic performances, and La, Pr, Sm, Eu, and Er realized conversions of 28.2%, 25.7%, 30.2%, 36.3% and 25.2%, respectively, with **EHN** as a single product (entries 10–15). Nevertheless, $Ce(OTf)_3$ was an exception that afforded a confused distribution of products, just like $Cu(OTf)_2$ and $Fe(OTf)_3$. It was notable that $Eu(OTf)_3$-catalyzed nitration could also become disorderly in the absence of urea (entry 16). Prolonging the reaction time increased the conversions. $Eu(OTf)_3$ achieved a higher conversion (56.3%) than the triflates of Sm, alkaline earth metal Ca and Group VA metal Bi (entries 16–19) in the course of 10 h.

Table 1 Screening of metal triflates by 2-ethylhexanol nitration[a]



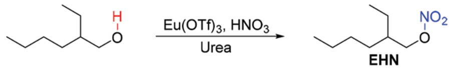
Entry	$M(OTf)_n$	Conv. [b] (%)	Select. [b] (%) EHN	EHA	IOA	EHEH
1[c]	—	86.6	9.3	41.3	38.6	5.4
2[d]	—	4.9	>99	0	0	0
3	Na	9.0	>99	0	0	0
4	Mg	18.6	>99	0	0	0
5	Ca	23.7	>99	0	0	0
6	Ba	22.9	>99	0	0	0
7	Bi	21.2	>99	0	0	0
8	Cu	68.1	35.9	6.0	50.9	7.2
9	Fe	47.0	11.3	47.5	10.1	31.0
10	La	28.2	>99	0	0	0
11	Ce	64.7	13.2	13.0	66.4	7.4
12	Pr	25.7	>99	0	0	0
13	Sm	30.2	>99	0	0	0
14	Eu	36.3	>99	0	0	0
15	Er	25.2	>99	0	0	0
16[e]	Eu	94.4	6.5	27.3	54.7	4.8
17[f]	Eu	56.3	>99	0	0	0
18[f]	Sm	47.2	>99	0	0	0
19[f]	Ca	36.4	>99	0	0	0
20[f]	Bi	31.6	>99	0	0	0

[a] Reaction conditions: 2-ethylhexanol (2.5 mmol), $M(OTf)_n$ (5 mol% based on 2-ethylhexanol), HNO_3 (1.4 equiv.), urea (5 mol%, based on HNO_3 loading), 2 mL of DCE, 90 °C, and 5 h. [b] GC yields. [c] $M(OTf)_n$ and urea free. [d] $M(OTf)_n$ free. [e] Urea free. [f] For 10 h.

To further optimize the reaction conditions, we evaluated the solvent, the loading amounts of both $Eu(OTf)_3$ and urea, temperature, and reaction time (Table 2). As can be seen, the nitration worked more preferably in nonpolar solvents than in low-polarity solvents. The conversions achieved in cyclohexane, *n*-heptane and isooctane were higher than those achieved in DCE and dichloromethane (entries 1–5, Table 2). In polar acetonitrile and ethyl acetate, the conversions reached 88.3% and 86.3%, but the selectivity of **EHN** decreased to 65.1% and 1.4%, respectively (entries 6 and 7, Table 2). GC-MS detected that **EHEH** became the main product, showing that oxidation, hydrolysis and esterification took place together with Lewis acid $Eu(OTf)_3$. In the cyclic polar solvents dioxane and tetrahydrofuran, the reactions occurred in a disorderly manner, where ring decompositions were observed (entries 8 and 9, Table 2). So, cyclohexane was chosen as the solvent in the further optimal tests. It was not unexpected to find that the more loading amounts of $Eu(OTf)_3$ resulted in faster rates of nitrations (entries 10–13, Table 2). In the course of 10 h, 10 mol% $Eu(OTf)_3$ realized 88.2% conversion. Prolonging the time to 15 h increased the conversion to 91.0% (entry 14, Table 2). Increasing the temperature increased the reaction rate, and 95 °C seemed to be the preferable temperature for the nitration of 2-ethylhexanol to **EHN** (entries 15–18, Table 2). Temperatures of 100 °C and above could result in the oxidation of HNO_3. The loading amount of the stabilizer urea showed an obvious influence on the nitration. More urea would slow down the reaction, and less urea would lead to the occurrence of side reactions (entries 19–21, Table 2). The preferable amount was 3 mol% (based on HNO_3), which provided a 98.5% yield of **EHN**.

For nitration, the complete consumption of HNO_3 will lead to a simple separation of products and avoid the generation of acidic waste. Table 3 presents the results of the nitration of 2-ethylhexanol with different amounts of HNO_3. As can be seen, the more the HNO_3 used, the faster the reaction (entries 1–5, Table 3). Employing 0.95 equivalents of HNO_3 as the nitrating reagent was intended to investigate whether HNO_3 could be consumed completely. The method was surveying the pH value of the reaction mixture. When the pH increased to 2, HNO_3 was deemed to be nearly exhausted. When the nitration with 0.95 equivalents of HNO_3 proceeded for 12 h, the conversion reached 92.1% and the pH less than 1 (entry 6). This meant that at the later stage of nitration the rate slowed down. The presumable causes could be that the residual HNO_3 became so little that the nitration hardly ever took place. The

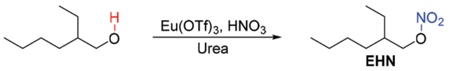
Table 2 Optimization of conditions for EHN preparation with $Eu(OTf)_3$[a]



Entry	$Eu(OTf)_3$ (mol%)	Solvent	T (°C)	Urea [c] (mol%)	Conv. [b] (%)	Select. [b] (%)
1	5	DCE	90	5	56.3	>99
2	5	Dichloromethane	90	5	43.6	>99
3	5	Cyclohexane	90	5	63.1	>99
4	5	*n*-Heptane	90	5	64.3	>99
5	5	Isooctane	90	5	60.8	>99
6	5	Acetonitrile	90	5	88.3	65.1
7	5	Ethyl acetate	90	5	86.3	1.4
8	5	Dioxane	90	5	39.3	4.1
9	5	Tetrahydrofuran	90	5	9.4	5.4
10	2.5	Cyclohexane	90	5	52.3	>99
11	5	Cyclohexane	90	5	64.3	>99
12	7.5	Cyclohexane	90	5	71.4	>99
13	10	Cyclohexane	90	5	88.2	>99
14[d]	10	Cyclohexane	90	5	91.0	>99
15	10	Cyclohexane	80	5	63.2	>99
16	10	Cyclohexane	90	5	88.2	>99
17	10	Cyclohexane	95	5	91.0	>99
18	10	Cyclohexane	100	5	98.9	94.1
19	10	Cyclohexane	95	1.5	99.1	97.8
20	10	Cyclohexane	95	3	98.5	>99
21	10	Cyclohexane	95	5	91.0	>99

[a] Reaction conditions: 2-ethylhexanol (2.5 mmol), HNO_3 (1.4 equiv.), 2 mL of solvent, and 10 h. [b] GC yields. [c] Based on HNO_3 loading. [d] For 15 h.

Table 3 Nitration of 2-ethylhexanol with different amounts of HNO_3[a]



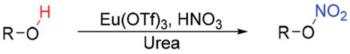
Entry	HNO_3 (equiv.)	t (h)	Conv. [b] (%)	pH
1	0.95	10	90.3	<1
2	1.0	10	93.9	<1
3	1.02	10	96.9	<1
4	1.2	10	98.5	<1
5	1.4	10	98.5	<1
6	0.95	12	92.1	<1
7	0.95	24	94.8	3
8	1.0	24	99.2	2

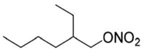
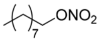
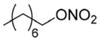
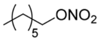
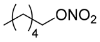
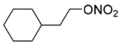
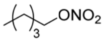
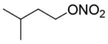
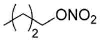
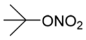
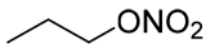
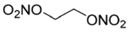
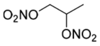
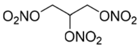
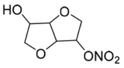
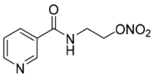
[a] Reaction conditions: 2-ethylhexanol (2.5 mmol), $Eu(OTf)_n$ (10 mol%), 3 mol% urea (based on HNO_3), 2 mL of cyclohexane, and 95 °C. [b] GC yields.

reaction could be completed by prolonging the time to 24 h, wherein the pH rose to 3 (entry 7). By prolonging the time to 24 h and employing 1.0 equivalent of HNO_3, the nitration realized 99.2% GC conversion (entry 8). These implied that HNO_3 could be almost depleted in the nitration.

Recognizing the successful performance of $Eu(OTf)_3$, we sought to further explore its generality with various alcohols (Table 4). It was delightful to find that the gram-scale test of 2-ethylhexanol nitration could realize a near complete conversion, and afforded a 98% isolated yield of **EHN** with over 99% purity which was obtained by simple liquid separation, water washing and distillation to remove the solvent after the reaction accomplishment (entry 1, Table 4), illustrating its practicability. Similar results were obtained for the nitrations of alcohols with more than six carbons, and *n*-nonanol, *n*-octanol, *n*-heptanol, *n*-hexanol and cyclohexylethanol provided over 95% isolated yield, respectively (entries 2–6). However, a reddish brown gas appeared in the reaction mixture, and the corresponding oxidative products by HNO_3 were detected in the nitration of pentanol whether it was linear or branched (entries 7 and 8). The same phenomena occurred in all nitrations of alcohols with less than five carbons. The smaller the alcohol was, the more the oxidation occurred. In small polyhydric alcohols, oxidation became the main reaction. It might be explained that, since smaller alcohols have higher hydrophilicity and solubilities in HNO_3 solution, aqueous oxidation is more likely to occur than nitration in nonpolar solvents. In order to improve the yield, more amounts of both urea and HNO_3, and lower temperature were employed in further nitrations of small and polyhydric alcohols (entries 7–15). The nitrations of *n*-pentanol, iso-pentanol, and *n*-butanol realized over 90% isolated yields, respectively. However, iso-butanol, *n*-propanol, 1,2-ethanediol, and 1,2-propanediol provided moderate yields in all the cases, and the isolated yield of the most hydrophilic glycerol nitration was as low as 10%. Unfortunately, a Lewis-acid-catalyzed ring-opening reaction was observed in isosorbide nitration which provided a 41% isolated yield of **ISMN** (entry 15). The nitration of *N*-2-hydroxyethyl-nicotinamide, the synthetic intermediate of the drug nicorandil, was conducted in excess HNO_3 due to its poor solubility in organic solvents, and an 86% isolated yield of nicorandil was obtained (entry 16).

Table 4 Nitration of various alcohols[a]



Entry	Alcohol	Urea [b] (mol%)	T (°C)	t (h)	Product	Yield [c] (%)
1[d]	Iso-octanol	3	95	10		98
2	*n*-Nonanol	3	95	14		96
3	*n*-Octanol	3	95	12		96
4	*n*-Heptanol	3	95	14		95
5	*n*-Hexanol	3	95	10		96
6	Cyclohexylethanol	3	95	16		97
7[e]	*n*-Pentanol	5	85	8		92
8[e]	Iso-pentanol	5	95	10		95
9[e]	*n*-Butanol	5	80	10		90
10[e]	Iso-butanol	5	55	10		60
11[e]	*n*-Propanol	5	60	10		62
12[e]	1,2-Ethanediol	5	70	24		60
13[e]	1,2-Propanediol	5	70	24		51
14[e]	Glycerol	5	80	24		10
15[f]	Isosorbide	3	90	24		41
16[g]	*N*-2-Hydroxyethyl-nicotinamide	3	70	6		86

[a] Reaction conditions: alcohol (2.5 mmol), $Eu(OTf)_3$ (10 mol%), HNO_3 (1.02 equiv.), and 2 mL of cyclohexane. [b] Based on HNO_3. [c] Isolated yield. [d] 3.25 g of 2-ethylhexanol (25 mmol), and 20 mL of cyclohexane. [e] HNO_3 (2.2 equiv.). [f] DCE instead of cyclohexane. [g] 5 equiv. of HNO_3 instead of cyclohexane.

Conclusions

We successfully developed a novel, efficient and versatile methodology to prepare nitroesters that used europium triflate as a catalyst and commercial nitric acid directly as the nitrating agent. Such nitration was suitable for the synthesis of various aliphatic nitroesters from the corresponding alcohols under mild conditions. The reaction can be conducted on a gram scale with good reaction efficiency, and it provides a practical protocol from both economic and environmental points of view, as well as operational ease.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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