Ceric ammonium nitrate (CAN)—a useful catalyst for the rapid and high-yield esterification of carboxylic acids and alcohols with special reference to steroid and other multi-functional natural products

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Ceric ammonium nitrate (CAN) acts as a versatile catalyst for the esterification of carboxylic acids and alcohols, including steroids and other multi-functional natural products, in excellent yields under mild and convenient reaction conditions.

The method of protection of hydroxyl and carboxyl groups by making their esters is an important reaction in synthetic organic chemistry.[1,2] Although a number of esterification techniques have been reported in the literature, a great need still exists for a simple and mild procedure for this transformation,[3,4] since most of these methods involve the use of toxic reagents and catalysts, *viz*., acid chlorides, acid anhydrides and catalysts like pyridine and its derivatives: DMAP,[5–7] *etc*. Some other catalysts used in esterification are $Bu^n_4N^+F^-$,[8] DBU,[9] $(C_8H_{17})_3N^+MeCl^-$,[10] $Ph_3P(OSO_2CF_3)_2$[11] and tributylphosphine.[12] Besides these examples, recent work on esterification includes the application of various metal triflates, *viz*., $Sc(OTf)_3$,[13,14] $Yb(Otf)_3$,[15] TMSOTf,[16] *etc*.

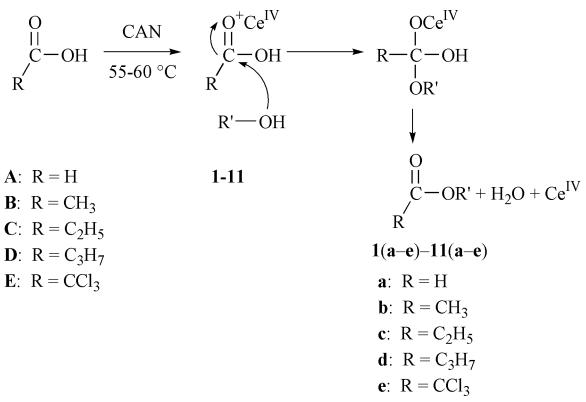
Recently, the development of new synthetic methods and reactions using new and environmental friendly reagents is becoming more attractive. We describe here a very simple method of esterification of carboxylic acids using ceric ammonium nitrate (CAN) as the catalyst, which eliminates the use of various toxic and costly catalysts and reagents generally used in esterification processes. The reaction can be carried out simply under mild heating of a mixture of a carboxylic acid and an alcohol as such, or in an organic solvent in the presence of a catalytic amount of CAN, giving excellent yield of the ester. The results obtained for various alcohols (**1**–**11**) with a number of different carboxylic acids (**A**–**E**) using CAN are given in Table 1. The esterification of both primary and secondary alcohols based on steroid and other multifunctional natural products, as shown in Table 1, proceeded smoothly and the yields of all the esters [**1(a–e)**–**11(a–e)**], including the sterically hindered macrolide **6**, were very high. Therefore, ceric ammonium nitrate can be regarded as an efficient catalyst for the rapid and high-yield esterification of carboxylic acids with primary and secondary alcohols. Under similar reaction conditions tertiary alcohols and aromatic acids are not esterified. Thus, when tertiary alcohol **9** was treated with carboxylic acids **A**–**E**, or when the aromatic acid **6′** was subjected to esterification with methanol or ethanol, no reaction took place and the starting materials were recovered quantitatively.

CAN is known for effectuating various chemical transformations, such as nitration,[23] nitroacetamidation,[24] cleavage of acetals and ketals,[25,26] formation of the "red complex" with alcohols by co-ordination with oxygen,[27] *etc*. Although the actual mechanistic details of the present esterification process are not known, a possible path for this reaction, as given in Scheme 1, can be rationalised on the basis of some experimental findings: (*i*) catalytic amounts only of CAN are sufficient for completion of the reaction and (*ii*) under our experimental conditions, when an alcohol (**1**–**11**) was heated (55–60 °C) with CAN in chloroform for a considerable period of time, no reaction was observed and both reactants were recovered unchanged. Further work on the action of CAN in a Baeyer–Villiger type oxidation is in progress.

All the esters gave satisfactory IR, NMR and mass spectral data. In the IR spectra all the alcohols (**1**–**11**) after esterification [to give **1(a–e)**–**11(a–e)**] exhibited an additional band at 1725–1735 cm^{-1} corresponding to the ester function formed. In the ^1H NMR spectra, all the formate esters (**1a**–**11a**) exhibited a singlet at 7.8–8.1 ppm for the HCO proton, all acetates (**1b**–**11b**) displayed an additional three-proton singlet at 1.9–2.1 ppm for the ester protons, all the propionate esters (**1c**–**11c**) showed an additional multiplet at 2.25–2.35 ppm for the OCH_2 protons and a methyl signal at 1.1–1.25 ppm, while all the butyric acid esters (**1d**–**11d**) exhibited an additional multiplet at 2.20–2.35 ppm for the OCH_2 protons, a methylene signal at 1.20–1.25 ppm and a methyl signal at 0.95–1.1 ppm. In addition, all the esters [**1(a-e)**–**11(a-e)**] displayed the correct molecular ion (M^+) in the mass spectra.

Experimental

Melting points were determined in capillaries and are uncorrected. IR spectra were recorded in a Perkin–Elmer 237 B grating spectrophotometer on chloroform solutions. ^1H NMR spectra were recorded on a Varian T-60 NMR instrument in deuterio-chloroform using TMS as the internal standard. Mass spectra were scanned on an INCOS 50 GC-MS instrument. TLC was performed on silica gel (E. Merck) and the plates were activated at 100 °C before use.



Scheme 1

Table 1 Esterification of steroid and other natural product based alcohols with carboxylic acids **A**–**E**[a] catalysed by ceric ammonium nitrate (CAN)

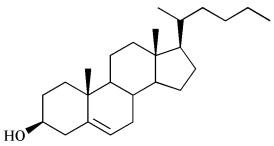
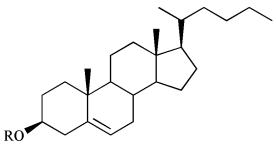
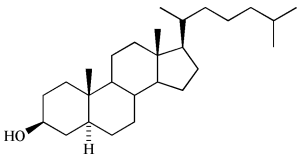
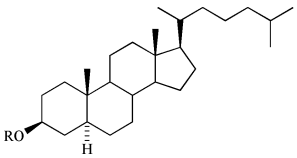
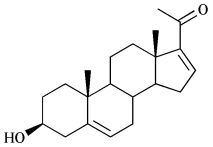
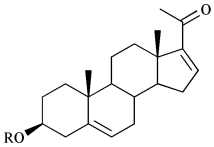
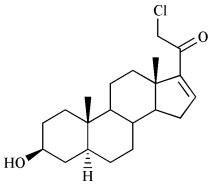
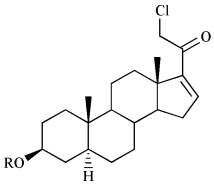
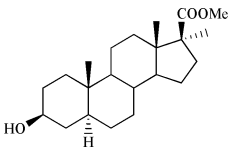
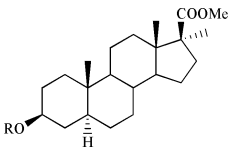
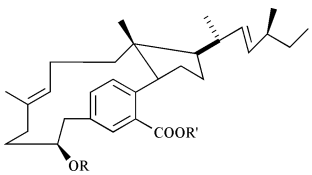
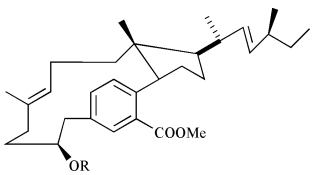
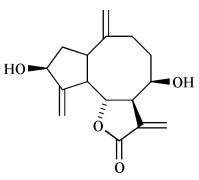
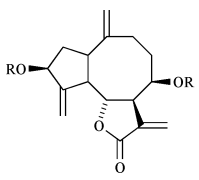
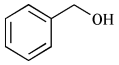
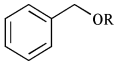
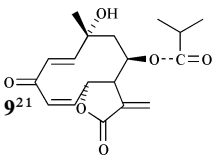
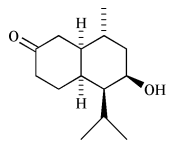
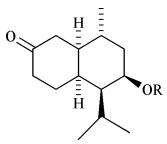
Alcohol[a]	Ester[a]	Yield[b] (%)	m/z[b]	mp[b]/°C
				
		95	414	112
		98	428	114
		90	442	113
		90	456	97
1	**1a**–**e**	95	530, 532[c]	130
				
		90	416	117
		98	430	110
		90	444	109
		92	458	99
2	**2a**–**e**	96	532, 534[c]	130
				
		95	342	180
		98	356	170
		92	370	168
		90	384	150
3[17]	**3a**–**e**	95	458, 460[c]	201
				
		90	378	157
		98	392	154
		90	406	150
		88	420	135
4[18]	**4a**–**e**	95	494, 496[c]	180
				
		95	376	—
		98	390	—
		93	404	—
		90	418	—
5[18]	**5a**–**e**	95	492, 494[c]	—
				
		98	508	100
		93	522	98
		90	536	92
		92	550	80
6[19] R = H, R′ = Me **6′** R = OAc, R′ = H	**6a**–**e**[d]	95	624, 626[c]	130
				
		90	278	—
		98	306	—
		95	334	—
		92	362	—
7[e, 20]	**7a**–**e**	90	570, 572[c]	—
				
		95	136	—
		98	156	—
		95	164	—
		92	178	—
8	**8a**–**e**	95	252, 254[c]	—
	—[d]	—	—	—
9[21]				

Table 1 Continued

Alcohol[a]	Ester[a]	Yield[b] (%)	m/z[b]	mp[b]/°C
				
		98	266	—
		93	280	—
		90	294	—
		92	308	—
10[22]	**10a–e**	95	382, 384[c]	—
				
		98	118	—
		93	146	—
		90	174	—
		92	202	—
11[e]	**11a–e**	95	350, 352[c]	—

[a] The reactant carboxylic acids and alcohols, along with the product esters, are defined on Scheme 1. [b] Yields of the pure isolated esters, their molecular ions $[M]^+$ and the melting point of all solid esters are given in the order ***N*a–e** within each group corresponding to the reaction of alcohol ***N*** with the 5 carboxylic acids **A–E**. [c] The **e** esters show two molecular ion peaks due to the ^{35}Cl and ^{37}Cl isotopes. [d] No reaction was observed with **6′** or with **9**. [e] The diester was formed in all cases.

General procedure for the esterification of alcohols and carboxylic acids catalysed by ceric ammonium nitrate

A mixture of an alcohol (1.5 mmol) and a carboxylic acid (1.5 mmol) was allowed to heat at a temperature of 55–60 °C in the presence of ceric ammonium nitrate (0.10 mmol) for a period of 30–60 min. The reaction was followed by TLC. Chloroform was added if necessary to dissolve the acid or alcohol used in the reaction. To work up the reaction the mixture was poured into cold water (100 ml) and extracted with petroleum ether (2 × 100 ml). The organic extract, after drying over anhydrous sodium sulfate, was evaporated under reduced pressure to obtain the product ester, which was further purified by preparative TLC. Since the reactions with all the substrates were carried out on a small scale with a minimum amount of CAN, the catalyst could not be recycled and went into the aqueous phase during work-up.

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References

1 P. J. Kocienski, in *Protecting Groups*, ed. D. Enders, R. Noyori and B. M. Trost, Thieme, Stuttgart, 1994, pp. 119–154.
2 (*a*) T. W. Greene, in *Protecting Groups in Organic Synthesis*, ed. J. F. W. McOmie, Wiley, New York, 1981, pp. 50–66; (*b*) E. Haslam, *Protecting Groups in Organic Chemistry*, ed. J. F. W. McOmie, Plenum, London, 1973, p. 183.
3 E. Haslam, *Tetrahedron*, 1980, **36**, 2409 and references cited therein.
4 R. Nakao, K. Oka and T. Fukumoto, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1267.
5 T. Mukaiyama, M. Usui, E. Shimada and K. Saigo, *Chem. Lett.*, 1975, 1045.
6 A. Hassner and V. Alexandrian, *Tetrahedron Lett.*, 1978, 4475.
7 (*a*) A. Hassner, V. Alexandrian and L. Krepski, *Tetrahedron*, 1978, **34**, 2069; (*b*) G. Hofle and W. Steiglich, *Tetrahedron Lett.*, 1970, 4727.
8 S. L. Beaukage and K. K. Ogilvie, *Tetrahedron Lett.*, 1977, 1691.
9 N. Ono, T. Yamada, T. Saito, K. Tanaka and A. Kaji, *Bull. Chem. Soc. Jpn*, 1978, **51**, 2401.
10 V. Bocchi, G. Casanti, A. Dossena and R. Marchelli, *Synthesis*, 1979, 957.
11 J. B. Hendrickson and S. M. Schwartzman, *Tetrahedron Lett.*, 1975, 277.
12 E. Vedegs, N. S. Bennett, L. M. Conn, S. T. Diver, M. Gingrass, S. Lin, P. A. Oliver and M. J. Peterson, *J. Org. Chem.*, 1993, **58**, 7286.
13 K. Ishihara, M. Kubota, H. Kurihara and H. Yamamota, *J. Am. Chem. Soc.*, 1995, **117**, 4413; K. Ishihara, M. Kubota, H. Kurihara and H. Yamamota, *J. Am. Chem. Soc.*, 1995, **117**, 6639.
14 K. Ishihara, M. Kubota, H. Kurihara and H. Yamamota, *J. Org. Chem.*, 1996, **61**, 4560.
15 (*a*) A. G. M. Barret and D. C. Braddock, *Chem. Commun.*, 1997, 351; (*b*) T. Hanamoto, Y. Sugimoto, Y. Yakoyama and J. Inanaga, *J. Org. Chem.*, 1996, **61**, 4491.
16 P. A. Porocopiou, S. P. D. Baugh, S. S. Flack and G. G. A. Inglis, *J. Org. Chem.*, 1998, **63**, 2342.
17 P. K. Chowdhury, M. J. Bordoloi, N. C. Barua, P. K. Goswami, H. P. Sarmah, R. P. Sharma, A. P. Barua, R. K. Mathur and A. C. Ghosh, *US Pat.* 5,808,117, 1998; *Indian Pat.* 1645/DEL, 1994.
18 (*a*) P. Borah, M. Ahmed and P. K. Chowdhury, *J. Chem, Res.* (*S*), 1998, 238; (*b*) P. Borah, M. Ahmed and P. K. Chowdhury, *J. Chem. Res.* (*M*), 1998, 1173; (*c*) P. Borah and P. W. Chowdhury, *J. Chem. Res.* (*S*), 1996, 502.
19 P. K. Chowdhury, A. Prelle, D. Schomburg, M. Thielmann and E. Winterfeldt, *Liebigs Ann. Chem.*, 1987, 1095.
20 A. K. Singhal, P. K. Chowdhury, R. P. Sharma, J. N. Barua and W. Herz, *Phytochemistry*, 1982, **21**, 462.
21 P. K. Chowdhury, N. C. Barua, R. P. Sharma, G. Thyagarajan and W. Herz, *J. Org. Chem.*, 1980, **45**, 535.
22 V. S. Shukla, N. C. Barua, P. K. Chowdhury, R. P. Sharma, M. J. Bordoloi and U. Rychlewska, *Tetrahedron*, 1986, **42**, 1157.
23 J. R. Hewe, K.-L. Chen and S. Anathan, *J. Chem. Soc., Chem. Commun.*, 1994, 1425.
24 M. V. R. Reddy, B. Malhotra and Y. D. Vanker, *Tetrahedron Lett.*, 1995, **36**, 4861.
25 A. Ates, A. Gautier, B. Leroy, J. M. Plancher, Y. Quensel and E. Marko, *Tetrahedron Lett.*, 1999, **44**, 1299.
26 V. Nair, L. G. Nair, L. Balagopal and R. Rajan, *Indian J. Chem., Sect. B*, 1999, **38**, 1234.
27 (*a*) L. B. Young and W. Trahanovsky, *J. Am. Chem. Soc.*, 1969, **91**, 5060; (*b*) W. Trahanovsky, P. J. Flash and L. M. Smith, *J. Am. Chem. Soc.*, 1969, **91**, 5068.