Tandem Oxidation Processes: The Direct Conversion of Activated Alcohols into Esters and Amides

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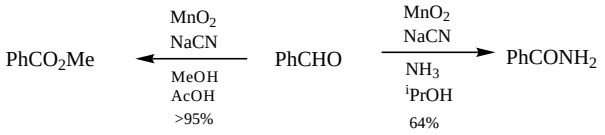
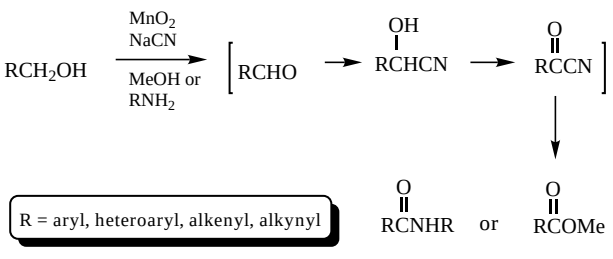
Abstract: The direct conversion of primary alcohols into methyl esters and amides using manganese dioxide and sodium cyanide with methanol or the appropriate amine is reported. These transformations, which proceed via an in situ four step, double oxidation sequence, have been applied to a range of benzylic, heterocyclic, allylic and propargylic alcohols.

Key words: oxidation, cyanide, cyanohydrin, acyl cyanide, one-pot

As part of a programme to design synthetically useful tandem oxidation processes, we have developed one-pot manganese dioxide-mediated transformations of primary alcohols giving alkenes,[1,2] imines,[3] amines,[3] oximes,[4] and nitriles.[5] In 1968, Corey, Gilman and Ganem reported a one-pot conversion of aromatic and unsaturated aldehydes into their corresponding methyl esters using manganese dioxide, acetic acid and sodium cyanide in methanol (Equation 1).[6] In 1971, Gilman extended this protocol to prepare amides from aromatic aldehydes and cinnamaldehyde (Equation 1).[7] In this Letter we report that activated alcohols can be directly transformed into ester or amides in a one pot, four step sequence (Equation 2), thereby extending the versatility of this methodology.



Equation 1



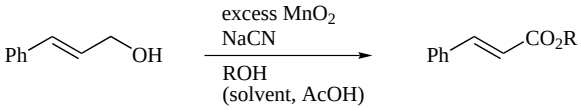
Equation 2

Our initial experiments involved the conversion of cinnamyl alcohol into methyl cinnamate (Table 1). We were delighted to find that the original conditions[6] gave the desired transformation, albeit rather slowly (84%, 2 d). We also established that the presence of acetic acid was not essential, although it did accelerate the process. We then explored the use of mixed solvents (containing 5 equivalents of methanol) and found that THF–MeOH produced a 70% yield after only 5 hours at reflux, and that the yield remained constant providing 15 equivalents of manganese dioxide and one equivalent of sodium cyanide were employed.[8] It is worth noting that the reaction still proceeded with as little as 0.2 equivalents of sodium cyanide, although the yield was reduced to 52%.[9]

Attempts to replace the methanol by other alcohols gave limited success; ethyl cinnamate was produced in 49% yield whereas the *iso*-propyl analogue was isolated in only 10% yield.

Following these preliminary studies, the optimum conditions (**A** and **B** in Table 1) were utilised with a range of activated alcohols (Table 2).[10] Conditions **B** were studied first as they gave the fastest transformation, and as can be seen, the procedure was successful with a range of aromatic, heterocyclic, alkynyl and alkenyl examples. Al-

Table 1 In Situ Oxidation-Esterification Reactions



Conditions	Time	Yield
20 MnO_2, 5 NaCN, 1.5 AcOH, MeOH, r.t.	2 d	84% (**B**)
20 MnO_2, 5 NaCN, MeOH, r.t.	3 d	78%
20 MnO_2, 5 NaCN, CH_2Cl_2–MeOH, Δ	17 h	72%
20 MnO_2, 5 NaCN, Et_2O–MeOH, Δ	16 h	68%
20 MnO_2, 5 NaCN, THF–MeOH, Δ	5 h	70%
15 MnO_2, 1 NaCN, THF–MeOH, Δ	5 h	70% (**A**)
15 MnO_2, 0.2 NaCN, THF–MeOH, Δ	5 h	52%
20 MnO_2, 5 NaCN, 1.5 AcOH, EtOH, r.t.	7 d	49%
20 MnO_2, 5 NaCN, 1.5 AcOH, *i*PrOH, r.t.	7 d	10%

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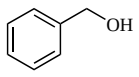
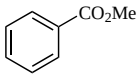
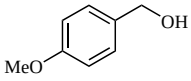
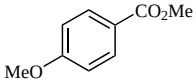
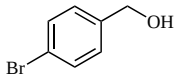
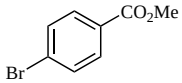
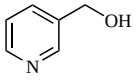
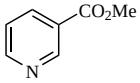
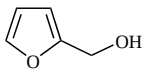
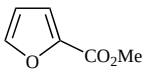
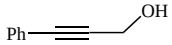
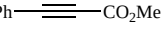
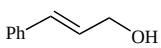
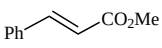
most all of the reactions went cleanly giving the product methyl ester in spectroscopically pure form without the need for chromatographic purification (i.e. after simple filtration and aqueous work-up). The isolated yields ranged from 46–70% but repeating those reactions with yields lower than 50% using conditions **B** greatly improved the efficiency, although, as expected, reaction times were increased (Table 2, entries iii and v).

Attempts to extend this methodology to unactivated alcohols such as decanol[1b] were unsuccessful (Method **A**, 99% recovered decanol after reflux for 20 hours).

Table 2 In Situ Oxidation-Esterification Reactions[a]

Entry	Alcohol	Product	Isolated Yield[a,b]
(i)			**A**: 53% (18 h)
(ii)			**A**: 57% (15 h)
(iii)			**A**: 46% (15 h) **B**: 80% (3 d)
(iv)			**A**: 64% (2 h)
(v)			**A**: 41% (20 h)[c] **B**: 77% (7 d)
(vi)			**A**: 66% (18 h)
(vii)			**A**: 70% (5 h)

[a] **Conditions A**:15 MnO_2, 1 NaCN, THF-MeOH, Δ;[8]
Conditions B: 20 MnO_2, 5 NaCN, 1.5 AcOH, MeOH, r.t.
[b] Yields refer to material isolated after filtration and solvent evaporation and shown to be essentially pure by NMR spectroscopy: after chromatographic purification isolated yields are 1–2% lower.
[c] NMR yield quoted as a trace of starting alcohol remained.

We next moved on to study amide formation. Preliminary studies were carried out using benzyl alcohol with *iso*-butylamine, and the optimum conditions developed (Equation 3).[11] Efficient conversion was achieved in THF (dichloromethane could also be used; 84% yield with 5 equiv amine), and yields were higher when the reaction was carried out at room temperature rather than reflux (at higher temperatures the corresponding imine[3] tended to predominate).

Equation 3

These conditions were applied to a range of substrates and amines (Table 3).[10] With benzyl alcohol (entry i), benzamide[12] and its *N*-methyl, *N*-*iso*-butyl and *N*,*N*-dimethyl derivatives were made in good to excellent yields via this one pot procedure. The use of diethylamine proved less satisfactory (25%), whereas pyrrolidine gave a 62% yield of the corresponding amide. This result suggests that the transformation is sensitive to steric hindrance, a hypothesis reinforced by the observation that the yield with *tert*-butylamine was less than 5%.

The process also worked well with electron rich and electron poor benzylic alcohols (entries ii and iii), and with pyridine, thiophene and furan examples (entries iv–vi). To date, we have not obtained practical yields with allylic and propargylic alcohols, in part due to apparent Michael addition of cyanide,[13] but success was achieved with an unactivated alcohol, tetrahydrofurfuryl alcohol (entry vii).

In conclusion, we have successfully developed straightforward one-pot procedures for the conversion of activated primary alcohols into methyl esters and amides. The procedure is mild and practically straightforward, does not require anhydrous conditions, and affords good to excellent yields of the products after a simple filtration-aqueous work-up. We are currently optimising and extending these processes, and looking at applications in natural product synthesis.

Acknowledgement

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References

(1) (a) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815. (b) Blackburn, L.; Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1999**, 1337. (c) Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 616. (d) Runcie, K. A.; Taylor, R. J. K. *Chem. Commun.* **2002**, 974.
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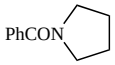
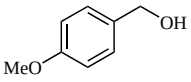
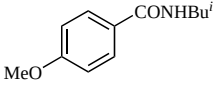
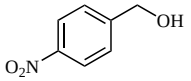
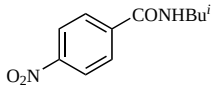
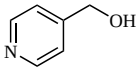
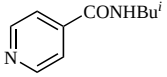
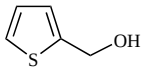
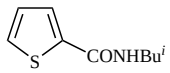
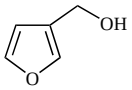
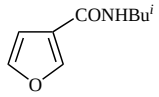
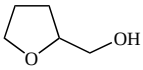
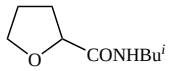
(3) Blackburn, L.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 1637.
(4) Kanno, H.; Taylor, R. J. K. *Synlett* **2002**, 1287.
(5) McAllister, G. D.; Wilfred, C. D.; Taylor, R. J. K. *Synlett* **2002**, 1291.
(6) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
(7) Gilman, N. W. *J. Chem. Soc., Chem. Commun.* **1971**, 733.
(8) (a) To a mixture of cinnamyl alcohol (134 mg, 1 mmol), sodium cyanide (49 mg, 1 mmol) and activated manganese dioxide (Aldrich 21764-6, 1.31 g, 15 mmol) stirring in tetrahydrofuran (10 mL), was added methanol (0.2 mL, 5 mmol). The reaction was heated to reflux and left to stir for 5 hours. The resulting mixture was then filtered through Celite® and the solvent removed under reduced pressure. Extraction with dichloromethane (50 mL), was followed by washing with water (2 × 10 mL) and then saturated sodium chloride solution (10 mL), before drying over magnesium sulfate. Filtration and removal of solvent in vacuo gave methyl *trans*-cinnamate (113 mg, 70%), as light yellow

Table 3 In Situ Oxidation-Amide Formation[a]

Entry	Alcohol	Amine	Product	Isolated Yield[a,b]
(i)		NH_3 (4 equiv)	$PhCONH_2$	53%
		$MeNH_2$ (2 equiv)	PhCONHMe	69%
		i$BuNH_2$ (5 equiv)	PhCONHBu^i	86%
		Me_2NH (5 equiv)	$PhCONMe_2$	73%
				62%
(ii)		*i*$BuNH_2$ (5 equiv)		81%
(iii)		*i*$BuNH_2$ (5 equiv)		77%[c]
(iv)		*i*$BuNH_2$ (5 equiv)		65%
(v)		*i*$BuNH_2$ (5 equiv)		64%
(vi)		*i*$BuNH_2$ (5 equiv)		59%
(vii)		*i*$BuNH_2$ (5 equiv)		45%[d]

[a] 30 MnO_2, 1 NaCN, THF, r.t., 23–26 h.[11]
[b] Isolated yields after chromatographic purification.
[c] 17 h (73% for 5 h).
[d] Using 40 equiv MnO_2 for 2 d.

crystals, which was pure according to ^{1}H NMR spectroscopy, mp 35 °C; lit.[14a] mp 35–36 °C. (b) Ethyl acetate, methyl acetate, acetonitrile and dimethyl formamide were also investigated as co-solvents without leading to improved yields.

(9) Alternatives to NaCN have also been investigated (e.g. KCN, LiCN, $NaCl_2O$, NaI, NaSCN, NaSCOMe, KOCN (using 2 equiv in each case). Only KCN (64%), LiCN (56%) and KOCN (6%) afforded methyl cinnamate.

(10) Most of the esters and amides are known compounds and were identified by comparison of their ^{1}H NMR spectra with published data. Novel compounds were fully characterised.

(11) A mixture of benzyl alcohol (108 mg, 1 mmol), *iso*-butylamine (0.5 ml, 5 mmol), sodium cyanide (49 mg, 1 mmol) and activated manganese dioxide (1.31 g, 15 mmol) was stirred in THF (15 mL) at r.t., After 30 min, a second batch of activated manganese dioxide (1.31 g, 15 mmol) was added and the reaction stirred for a further 23.5 h. The resulting mixture was then filtered through Celite® with additional dichloromethane being used to wash the Celite®. The combined organics were washed with water (2 × 20 mL) and then dried over magnesium sulfate. Filtration, removal of solvent in vacuo and chromatography on silica (petroleum ether–ether, 2:3) gave *N*-*iso*-butylbenzamide (153 mg, 86%), as a white solid, which was pure according to ^{1}H NMR spectroscopy; mp 55.8–56.1 °C (lit.[14b] mp 54–56 °C).

(12) For an alternative manganese dioxide route to a limited range of carboxamides, which does not use sodium cyanide, see ref.[5]

(13) Preliminary studies indicate that improved yields can be obtained with allylic alcohols if low temperatures (0 °C) are employed; the use of hexane as solvent can also improve yields in some cases. Further studies are being carried out which will be included in a full paper.

(14) (a) Kendall, J.; Booge, J. E. *J. Am. Chem. Soc.* **1916**, *38*, 1712. (b) Gajda, T.; Zwierzak, A. *Synthesis* **1981**, 1005.