Communications

Dual Activation in the Esterification of Hindered Alcohols with Anhydrides Using $MgBr_2$ and a Tertiary Amine

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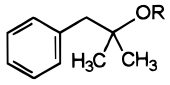
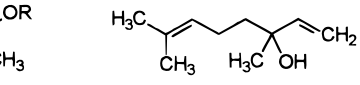
In the course of studies designed to evaluate reactive acylating agents, we observed that the combination of 2 equiv of $MgBr_2$ (anhydrous solution in THF), 3 equiv of a tertiary amine, and 2 equiv of benzoic anhydride benzoylated the secondary alcohol 1-phenylethanol within seconds (CH_2Cl_2, exotherm!) Secondary alcohol acylations were not pursued,[1] but we were interested to find that even the hindered pivalic anhydride reacts with alcohols using a similar "dual activation" procedure (tertiary amine + $MgBr_2$).[2] The activated pivalic anhydride reagent converted the sensitive tertiary alcohol **1** into the pivalate ester **2**[3] in 99% yield after 22 h at room temperature. The corresponding benzoylation (using benzoic anhydride) was much faster and gave 95% of the benzoate ester **3**[3] within 15 min! No elimination to *β*,*β*-dimethylstyrene was detected in either reaction.

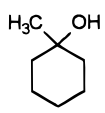


1 R= H
2 R= C(O)*t*-Bu



3 R= C(O)Ph
9 R= MgBr

4



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Several other examples were studied using alcohol−anhydride combinations that allow comparison with literature results for the preparation of the corresponding hindered esters (Table 1). Some optimization proved necessary in the case of anhydrides that contain enolizable α-hydrogens to minimize decomposition of the anhydride. This problem was encountered in attempts to prepare linalyl butyrate.[4] It was found that hindered amines are significantly better than triethylamine and that the order of mixing the reactants is important in the enolizable anhydrides. Thus, it was necessary to mix linalool (**4**) with $MgBr_2$ and the amine **prior** to addition of the anhydride (method A) to obtain a good yield. Better results were obtained with 1,2,2,6,6-pentamethylpiperidine (PMP) than with *i*-Pr_2NEt or triethylamine using 2 equiv of butyric anhydride, 1.5−2 equiv of amine, and 1.2−1.5 equiv of $MgBr_2$. No trace of the primary ester (geranyl butyrate) or the corresponding bromide was found (2% would have been detected). If all of the reagents were mixed and the alcohol was added subsequently (method B), decomposition of the anhydride increased as the degree of substitution at the α-carbon decreased. Acetic anhydride was most difficult and progressively better results were obtained with propionic, butyric, and isobutyric anhydrides. Method B was satisfactory for benzoylations and pivaloylations.

The dual activation method works well with phthalic anhydride and 1-methylcyclohexanol (**5**; Table 1, entry 2) although the reaction is significantly slower than analogous benzoylations. Succinoylation with **1** as the substrate did not proceed to completion (ca. 40% conversion to the hemisuccinate ester),[5] even with a large excess of succinic anhydride and extended reaction times (3 days). Cyclic anhydrides have been activated using the DMAP catalyst, but the reactions are slow compared to acyclic anhydrides.[6,7] Steglich and Höffle have reported that the hindered pivalic anhydride is not activated by DMAP.[7] We have confirmed this generalization using the tertiary alcohol **1** as the substrate (2 equiv of $[t\text{-BuC(O)}]_2O$ + 3 equiv of Et_3N + 2 equiv of DMAP; <1% conversion to **2** after 19 h at rt in CH_2Cl_2). Under similar conditions with DMAP, the benzoic anhydride affords 24% of the benzoate ester **3**. By comparison, the dual activation procedure is roughly 2 orders of magnitude faster. A comparison with the recently reported $Sc(OTf)_3$ method[8] was also made. An experiment with pivalic anhydride and **1** at 0 °C (5 equiv anhydride, 5 mol% scandium triflate, CH_3CN) gave significant elimination to *β*,*β*-dimethylstyrene as well as the pivalate ester **2**, but clean conversion to **2** was observed at −20 °C. The reaction was complete within 4 h, substantially faster than the dual activation procedure at room temperature. On the other hand, the $Sc(OTf)_3$-catalyzed benzoylation of **1** proved to be much slower. Conversion was too low to assay after 20 h at −20 °C and elimination accompanied benzoylation at 0 °C (22% benzoate **3**, 4% *β*,*β*-dimethylstyrene after 20 h at −20 °C and 11 h at 0 °C). The lower reactivity of aromatic anhydrides in the scandium triflate reactions was noted by Yamamoto *et al.* and was exploited for selective acylation using mixed acyl−aromatic anhydrides.[8] In contrast, dual activation appears to favor transfer of the aroyl subunit. Thus, the mixed pivalic, *p*-nitrobenzoic anhydride was reacted with the hindered alcohol **7**[9] (2 equiv of $MgBr_2$, 3 equiv of Et_3N, CH_2Cl_2, 19 h at rt), resulting in the *p*-nitrobenzoate ester **8** (80% isolated) and no pivalate by NMR assay (<5%). The scandium triflate selectivity pattern corresponds to the greater stability of alkyl-substituted vs aryl-substituted acylium ions,[10] although it is not known whether an acylium ion mechanism is involved.

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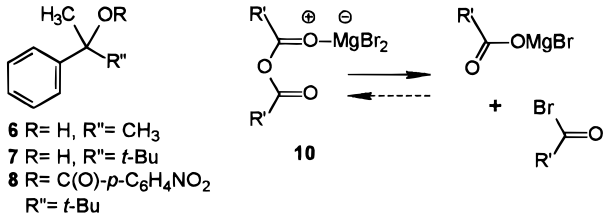
Table 1. Esterification of Alcohols (1 equiv) with Acid Anhydrides (2 equiv) + Amine + $MgBr_2$[a]

entry	ROH	$[R'CO]_2O$	amine (equiv)	$MgBr_2$, equiv	time	yield	lit. yield (%)	ref
1	1	$(PhCO)_2O$	Et_3N (3)	2, method B	15 min	95	85[b]	3
2	1	$(t\text{-}BuCO)_2O$	Et_3N (3)	2, method B	25 h	99	80[b]	3
3	6	$(i\text{-}PrCO)_2O$	Et_3N (3)	2, method A	25 min	99	60[c]	16
4	4	$(n\text{-}PrCO)_2O$	Et_3N (2)	1.5, method A	30 min	41	d	4
5	4	$(n\text{-}PrCO)_2O$	$i\text{-}Pr_2EtN$ (2)	1.5, method A	30 min	83	d	4
6	4	$(n\text{-}PrCO)_2O$	PMP (1.5)	1.2, method A	30 min	91	d	4
7	5	$C_6H_4(CO)_2O$	Et_3N (3)	2, method B	3 h	90	85[e]	17
8	7	PivOCOAr[f]	Et_3N (3)	2, method B	19 h	80	46[g]	18

[a] CH_2Cl_2 at rt. Method A: anhydride added last. Method B: alcohol added last. Method B has a small advantage in convenience in cases where the anhydride cannot decompose via enolization. [b] From the 1-ethoxyvinyl ester + **1**. [c] From the 1,1′-dimethylstannocene derivative of **6** + isobutyroyl chloride, 100 °C. [d] From butyric anhydride + H_3PO_4, no yield reported. [e] From the sodium alkoxide + phthalic anhydride. [f] Pivalic *p*-nitrobenzoic anhydride, generated *in situ*. [g] From the lithium alkoxide + *p*-nitrobenzoyl chloride.



To limit the number of plausible mechanistic possibilities, several control experiments were performed. When **1** was treated with $MgBr_2$ and $i\text{-}Pr_2NEt$, the ^1H NMR signals broadened and a small change in chemical shift was detected for the benzylic CH_2 group (CD_2Cl_2, δ 2.75 ppm for pure **1**, 2.86 ppm for the mixture). In addition, major new signals for the protonated amine appeared ($i\text{-}Pr_2NH\text{-}(+)\text{-}CH_2CH_3$, 3.15 ppm) at the expense of the neutral amine ($i\text{-}Pr_2NCH_2CH_3$, 2.45 ppm), but minor absorptions of the latter were still present. This evidence proves that proton transfer occurs from alcohol oxygen to nitrogen and that the potential equilibrium is slow on the NMR time scale. Evidently, formation of the Mg−O linkage pays the thermodynamic price for this conversion in spite of the expected pK_a disadvantage. Structure **9** is drawn for convenience, but the actual structure may be more complicated.

In another set of control experiments, the $MgBr_2$/THF complex was mixed with benzoic anhydride at rt and the ^{13}C spectrum was recorded. In addition to a signal at δ 163.4 ppm for the anhydride carbonyls, a smaller signal was seen at 165.9 ppm. When this mixture was rapidly filtered through silica gel, evaporated, and redissolved in CD_2Cl_2, signals assigned to benzoic anhydride (163.6 ppm, major), benzoyl bromide (166.1 ppm, minor), and benzoic acid (167 ppm, minor) were present and the characteristic odor of benzoyl bromide was apparent. The NMR assignments were supported by comparing the spectrum in $CDCl_3$ (benzoic anhydride, 162.3 ppm; benzoyl bromide 165.7 ppm) with published values.[11]

On the basis of the above information, it is likely that a magnesium alkoxide such as **9** is the nucleophile.[12] The identity of the electrophile is a more difficult problem. Benzoyl bromide is present in the reaction mixture, and its direct reaction with the magnesium alkoxide **9** is plausible. Some role for an *N*-acylammonium complex is also conceivable, but no evidence to support this conjecture could be found. Thus, it was observed that 2,6-dimethylpyridine is far more effective in the benzoylation of **1** (60% conversion in 2 h) than are other pyridine derivatives (percent conversion, time): pyridine (6%, 23 h), 2-picoline (32%, 19 h), 2-methylquinoline (54%, 19 h), 2,6-di-*tert*-butylpyridine (<3%, 24 h), *p*-(dimethylamino)-pyridine (DMAP; <2%, 25 h). A sufficient explanation for these trends is that a hindered base is needed to promote conversion to the magnesium alkoxide **9** and that no other role for the amine is required. The DMAP experiment can be understood if the highly nucleophilic amine binds irreversibly to $MgBr_2$ under these conditions. The other substituted pyridines are effective activating agents roughly in the order of their basicity as estimated from pK_a values of the pyridinium salts.[13] In contrast to DMAP, strongly basic, hindered amines such as $i\text{-}Pr_2NEt$ do not deactivate $MgBr_2$.

The $MgBr_2$ anhydride complex **10** (or a chelated equivalent) is probably involved in the anhydride activation sequence, and interconversion with the magnesium carboxylate and an alkanoyl or aroyl bromide appears likely on the basis of the data presented above. Conversion to the carboxylate oxygen−magnesium bond may provide the driving force for this process.[14] In view of the large number of potential variables, no further mechanistic interpretation will be offered at this time. However, it is clear that both the alcohol and the anhydride are activated by the combination of $MgBr_2$ and amine and that the combination of factors produces remarkable rate accelerations in the anhydride−alcohol reactions.[15]

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Supporting Information Available: Representative experimental procedures and NMR spectra of ester products (9 pages).

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(12) (a) A similar conclusion was reached by Evans *et al.*; see ref 2b. (b) Treatment of **1** with $MgBr_2$ *without* the amine also broadens the ^1H NMR signals and produces a small chemical shift change (benzylic CH_2, 2.81 ppm), presumably because of complex formation. Reaction of **1** with CH_3MgBr + added $MgBr_2$ (1 equiv) results in a CH_2 signal at 2.82 ppm.

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(15) (a) Hindered benzoates can be made using benzoyl triflate: Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875. (b) Benzoylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside using method B was nonselective and gave mainly the 2,3-di-*O*-benzoate. (c) Reaction of **1** (0.1 mmol), $Ph_2P(O)Cl$ (0.05 mmol), $EtN\text{-}i\text{-}Pr_2$ (0.15 mmol), and $MgBr_2$ (0.1 mmol) gave the phosphinate ester (80% yield, 20 min rt), but TsCl in place of $Ph_2P(O)Cl$ afforded only recovered **1**.

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