Reactivity of Acyl Derivatives toward Dialkoxytitanacyclopropane

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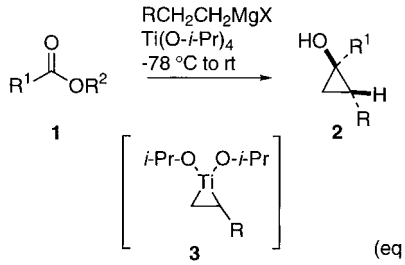
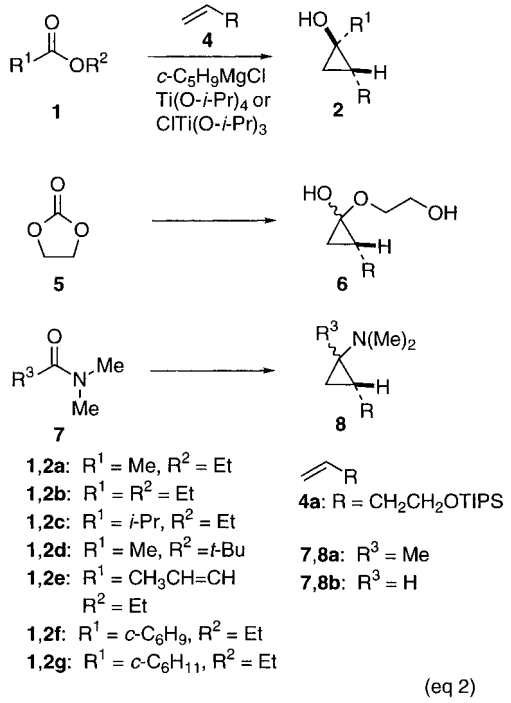
Several years ago, Kulinkovich and co-workers reported an efficient preparation of hydroxycyclopropanes by treatment of carboxylic esters with a suitable Grignard reagent in the presence of Ti(O-*i*-Pr)$_4$ (eq 1), in which



formation of a titanacyclopropane intermediate **3** was postulated.[2] We recently made a significant improvement over the original Kulinkovich protocol by exploiting facile olefin exchange which this presumed intermediate **3** undergoes with the terminal olefin **4**. Both intermolecular[3] and intramolecular[4,5] reactions of terminal olefins and esters have since been developed (eq 2). Moreover, further extension has successfully been made to other acyl derivatives. For example, use of ethylene carbonate and *N*,*N*-dialkyl carboxamide resulted in a new, general synthesis of cyclopropanone hemiketal **6** and tertiary aminocyclopropane **8**, respectively.[6,7] As a preliminary study of synthetic applications of these electron-donor substituted cyclopropanes in structurally complex natural products, we undertook to assess the relative reactivity of several acyl derivatives toward in situ prepared titanacyclopropane **3** by a series of competition experiments.

In a typical competition experiment, an equimolar mixture of two acyl derivatives (in THF) was treated with a limiting amount (0.8 equiv) of olefin **4a** (R = CH_2CH_2OTIPS) and an excess of cyclopentylmagnesium chloride in the presence of 0.8 equiv of ClTi(O-*i*-Pr)$_3$ at room temperature. Since the reaction rate is a function of both the reactivity and the concentration of the acyl compound, several competition experiments were also performed with smaller amounts (0.4 equiv each) of the olefin **4a** and ClTi(O-*i*-Pr)$_3$. Under the latter conditions, the concentrations of the two acyl reactants should



remain nearly constant and their product ratios would reflect their relative rates. Analysis of the product ratios from these experiments is tabulated in Table 1.[8] While cyclopropanation of the weakly electrophilic amide functionality proceeds rapidly at room temperature,[6b] the nucleophilic nature of the key intermediate **3** can be inferred from the observation that esters react even more rapidly than *N*,*N*-dialkyl carboxamides (entries 1−6). Modulation of the difference in intrinsic reactivity between esters and amides is possible by steric variation in substrate structures. For example, comparison of entry 1 with entries 2−6 reveals the sensitivity of cyclopropanation to steric effects where the rate decreases with increasing size of R^1 or R.[2] Similarly, the formamide **7b** reacts faster than the higher homologue **7a** (entry 7). The remarkable reversal in chemoselectivity in entry 6 can be explained by the increased steric interactions around the *tert*-butyl ester **1d**, especially compared to DMF. In entry 2 where a larger amount of the olefin **4a** was employed, a surprisingly large change in the product ratio was found and can be attributed to the concentration factor; as the reaction progresses, there will be a decreasing amount of the more reactive ester **1b**, resulting in the diminished product ratio. In other examples, however, no significant concentration effect was observed (entries 16 and 17). With regard to electronic (conjugative) effect, the presence of an α,β-unsaturated double bond results in only a modest attenuation in reactivity (entry 8). A large difference between ethyl priopionate (**1b**) and ethyl 1-cyclohexenecarboxylate (**1f**) (entry 9), taken together with the competition experiment (entry 10) between **1f** and ethyl 1-cyclohexanecarboxylate (**1g**), can best be attributed to steric effect.[9]

The reactivity of ethylene carbonate (**5**), as measured at 0 °C,[10] falls between that of ester and amide. However,

(1) A summer undergraduate research participant (summer 1996).
(2) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevskii, D. A. *Mendeleev Commun.* **1993**, 192 and references therein.
(3) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198.
(4) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291.
(5) (a) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079. (b) Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849.
(6) (a) Lee, J.; Kim, Y. G.; Bae, J. G.; Cha, J. K. *J. Org. Chem.* **1996**, *61*, 4878. (b) Lee, J.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 1584.
(7) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413.
(8) The product ratios given in Table 1 were obtained from ^{1}H NMR integrations and/or isolation yields.
(9) Surprisingly, no cyclopropanol product from methyl benzoate was found in the reaction mixture by employing either the original Kulinkovich method or the ligand exchange process.

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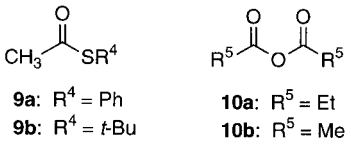
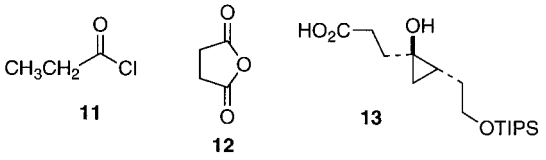


9a: R^4 = Ph
9b: R^4 = *t*-Bu

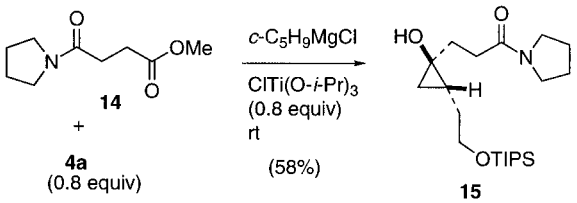
10a: R^5 = Et
10b: R^5 = Me



11 **12** **13**

the small difference in the relative reactivities among three acyl derivatives is surprising (entries 11−13). Extrapolation of the intrinsic (kinetic) reactivity of **5** from the product ratios may contain a certain margin for uncertainty due to its instability (which dictated that the reaction to be performed at 0 °C and is also reflected in overall lower yield).

Other acyl compounds such as thioester, anhydride, acid chloride, and *N*,*O*-dialkylhydroxamate also readily undergo cyclopropanation to afford the identical hydroxycyclopropanes that are derived from the corresponding esters. Thus, their relative reactivity profile was examined by use of different alkyl substituents for R^1 and R^5 (e.g., Me vs Et). As a general trend, comparable reactivity of these acyl derivatives was observed (entries 14−21). Surprisingly, the intrinsic reactivity of esters was found to be the highest, although the differences are rather insignificant. The product ratios from examples (entries 20 and 21) involving succinic anhydride (**12**) do not necessarily reflect the difference in their relative reactivity due to the instability of **12** under the reaction conditions.[11]



14 + **4a** (0.8 equiv) → **15**

(eq 3)

In summary, given similar steric considerations, the following general trend in the reactivity of various carbonyl groups is apparent in the cyclopropanation: ester ≅ acid chloride, anhydride ⩾ carbonate, thioester > formamide > carboxamide. For example, the greater reactivity of ester than amide is well illustrated in the exclusive formation of the cyclopropanol **15** from **14** (eq 3). Moreover, marked decrease in rate is observed for increasing steric interactions around the acyl group. Such information should be useful in the design of chemoselective preparations of electron-donor substituted cyclopropanes in the presence of other acyl derivatives.

(10) As previously noted in ref 6a, formation of cyclopropanone hemiketal from **5** proved to be very sensitive to reaction temperature, and 0 °C was the optimum temperature.

(11) For example, cyclopropanation of **12** alone gave the cyclopropanol **13** in 30% yield, accompanied by a significant amount of complex, unidentified byproducts.

Table 1. Competition Experiments of Two Acyl Compounds Towards 3[a]

entry	starting acyl derivatives	products	product ratio[b]	yield, %
	Ester vs Amide			
1	**1a** + **7a**	**2a** + **8a**	1:0	81
2	**1b** + **7a**	**2b** + **8a**	10.5:1 (4.2:1)[c]	73
3	**1c** + **7a**	**2c** + **8a**	2.0:1	78
4	**1d** + **7a**	**2d** + **8a**	4.3:1	78
5	**1a** + **7b**	**2a** + **8b**	2.2:1	76
6	**1d** + **7b**	**2d** + **8b**	1:1.6	72
	Acetamide vs Formamide			
7	**7a** + **7b**	**8a** + **8b**	1:8.6	70
	Ester vs α,β-Unsaturated Ester			
8	**1b** + **1e**	**2b** + **2e**	1.5:1	72
9	**1b** + **1f**	**2b** + **2f**	20:1	80
10	**1f** + **1g**	**2f** + **2g**	1:1	42
	Ester/Amide vs Carbonate			
11	**1a** + **5**	**2a** + **6**	1.5:1	59
12	**7a** + **5**	**8a** + **6**	1:1.8	60
13	**7b** + **5**	**8b** + **6**	1:1.0	51
	Ester vs Thioester			
14	**1b** + **9a**	**2b** + **2a**	1.8:1	64
15	**1b** + **9b**	**2b** + **2a**	1:0	65
	Ester vs Anhydride			
16	**1a** + **10a**	**2a** + **2b**	1.4:1 (1.7:1)[c]	81
17	**1b** + **10b**	**2b** + **2a**	1.6:1 (1.5:1)[c]	77
	Ester vs Acid Chloride			
18	**1a** + **11**	**2a** + **2b**	1.2:1	67
19	**10b** + **11**	**2a** + **2b**	1.8:1	68
	Use of Cyclic Anhydride			
20	**1a** + **12**	**2a** + **13**	1:0	69
21	**10b** + **12**	**2a** + **13**	6.5:1	85

[a] For experimental conditions, see text. With the exception of entries 11−13, all the remaining experiments were performed at room temperature. [b] The product ratios were obtained from ^{1}H NMR integrations and isolation. [c] The product ratios indicated by the parentheses were obtained by the use of 0.4 equiv each of **4a** and ClTi(O-*i*-Pr)$_3$.

Experimental Section

General Procedure for Competition Experiments. A solution of ethyl acetate (**1a**) (0.2 mL, 2.2 mmol), *N*,*N*-dimethylacetamide (**7a**) (0.2 mL, 2.2 mmol), and 1-(triisopropylsiloxy)-3-butene (0.4 g, 1.8 mmol) in THF (25 mL) was treated with ClTi(O-*i*-Pr)$_3$ (1.8 mL of 1.0 M solution in hexane). Commercially available cyclopentylmagnesium chloride (4.5 mL of 2.0 M solution in ether) was then added at room temperature during 20 min (syringe pump). The reaction mixture was then stirred for an additional 1 h and poured into water. The organic layer was separated, and the aqueous layer was extracted three times with ether. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to afford the crude product. Finally, purification was achieved by column chromatography on silica gel.

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