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New Process for the Preparation of Methyl Carbonates

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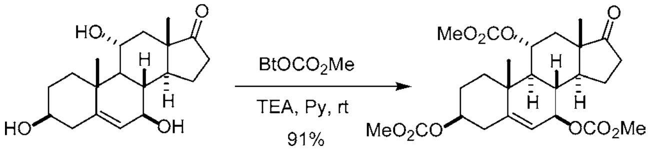
ABSTRACT



The methyl carbonate of HOBt was developed for the conversion of alcohols to carbonates. This method is superior to the use of methyl chloroformate or methyl pyrocarbonate, especially with more hindered alcohols. The reagent is a stable solid that is easily prepared on a multigram scale.

Carbonates may serve as protecting groups[2] or serve as superior leaving groups in a variety of metal-catalyzed transformations.[3] In connection with another project, we wished to take advantage of the carbonate as a protecting group and of its superior leaving group ability in a transition metal-catalyzed reaction on the tricarbonate **2c**. It soon became clear that the existing technology was inadequate for conversion of the triol **1** to the tricarbonate **2c**. Numerous attempts using methyl chloroformate and dimethyl pyrocarbonate failed to give good conversions to the desired tricarbonate **2c**. Table 1 summarizes some of these results showing that this transformation was indeed problematic. The cleanest reactions were obtained using TMEDA[4] as the base, and in this case the dicarbonate **2b** was formed with some selectivity; however, this reaction could not be scaled to make more than a few grams of material. In all these reactions, it appears that chloroformate decomposition is a problem and that the released methanol competes with the substrate **1**. The method using $MgBr_2/(MeO_2C)_2O$ was a derivative of a method used by Vedejs[5] for making hindered esters. These results led us to explore other possible carbonate transfer agents.

Table 1. Carbonate Formations with MeOCOCl and $(MeOCO)_2O$

entry	reagent	base	solvent	results
1	$(MeOCO)_2O$	DMAP	CH_2Cl_2	40% di, 44% tri
2	$(MeOCO)_2O$ $MgBr_2$	DIPEA	THF	1:1:1 mixture of mono/di/tri
3	MeOCOCl	Pyr	CH_2Cl_2	29−48% di, 30−17% tri
4	MeOCOCl	Pyr	Pyr	mixture of mono/di/tri
5	MeOCOCl	TMEDA	CH_2Cl_2	<78% di

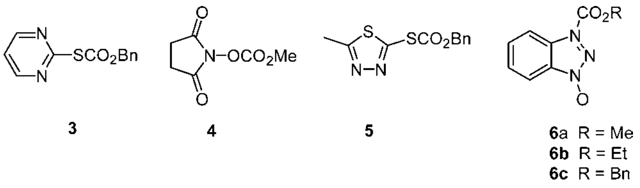


Figure 1. Potential carbonate-transfer agents.

Reagents **3−6** were prepared and tested as possible carbonate transfer agents (Figure 1). Of these only the HOBt-derived reagent **6**[6] was suitable for the preparation of the tricarbonate **2c**.[7] The thiadiazole reagent **5** was unstable, and

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agents **3** and **4** failed to transfer the carbonate using pyridine/TEA/DMAP. With 2 equiv/OH of **6a**, we were routinely able to obtain a 91% yield of the tricarbonate **2c** by simply adding water to the reaction mixture when TLC showed complete reaction and then filtering and drying. The solvent for this reaction proved to be important. Pyridine was the best solvent, but DMF could also be used although at the expense of rate and efficiency. The reaction proceeds only very slowly in solvents such as EtOAc and CH_3CN.

DMAP was beneficial as a catalyst as determined by measuring the heat flow using the Mettler–Toledo Multimax system. In this experiment, the heat of reaction for the preparation of carbonate **19b** was monitored by measuring $T_r - T_j$. Without DMAP, there is only minimal conversion on the basis of TLC. The curve in Figure 2 shows that when DMAP was added at about 3500 s to the reaction mixture, a rapid reaction ensues. The reaction was complete at 7400 s on the basis of the heat flow and the TLC.[8]

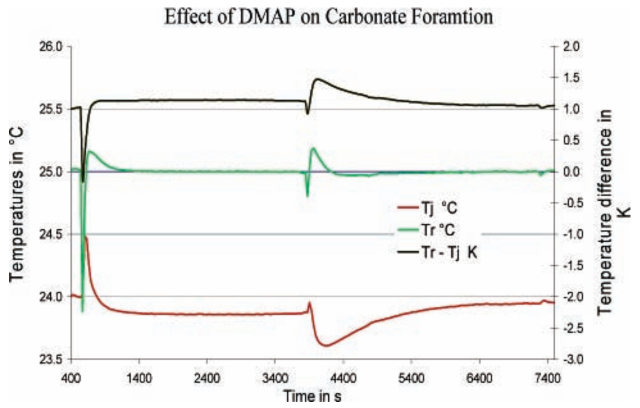
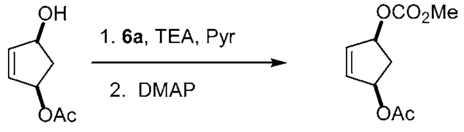


Figure 2. Heat flow for carbonate formation.



19a **19b**

The stability of **6a** was also examined using DSC, which shows melting at 152 °C followed by two exothermic events, one with an onset at 159 °C (111 J/g, heating rate = 10 °C/min) and one with an onset at 191 °C (1286 J/g). A DSC measured in pyridine (10:1 ratio) shows a small exotherm at 61.5 °C (14.4 J/g) and a larger one at 211.7 °C (118 J/g).

During the course of this work, we found that for the more hindered alcohols, 2 equiv of **6a** were required to drive the reaction to completion as a result of a competitive side reaction to form BtOMe **7**. It was determined that when **6a** and HOBt in pyridine/TEA were combined that **7** slowly forms with the liberation of CO_2. This was determined using a ReactIR and a mass spectrometer to monitor the CO_2 formation. The benzyl derivative **6c** is more prone to this

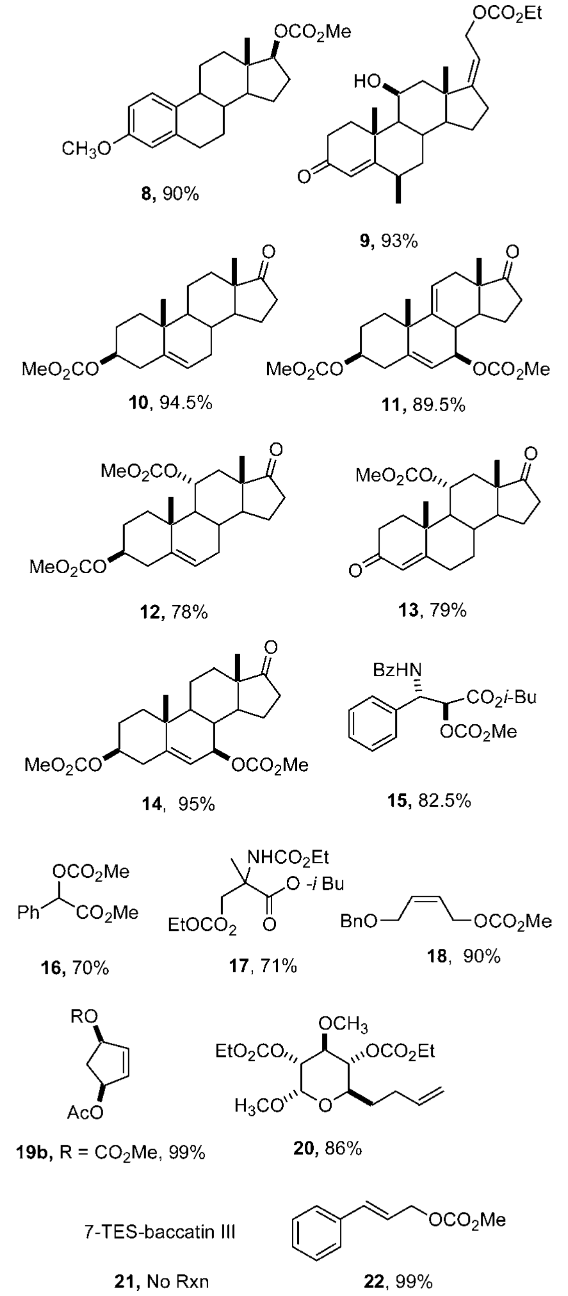


Figure 3. Results for the formation of carbonates.

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(3) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793.

(4) Sano, T.; Ohashi, K.; Oriyama, T. Synthesis **1999**, 1141.

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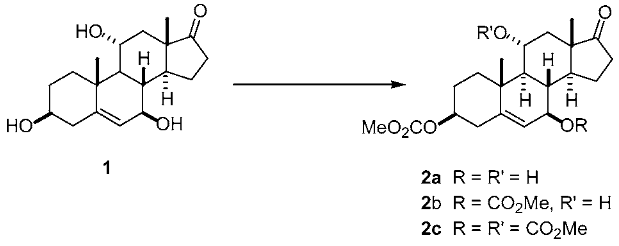
(6) These reagents are known to be *N*-acyl derivatives: Fruchier, A.; Elguero, J.; Hegarty, A. F.; McCarthy, D. G. *Org. Magn. Reson.* **1980**, *13*, 339. Singh, J.; Fox, R.; Wong, M.; Kissick, T. P.; Moniot, J. l.; Gougoutas, J. Z.; Maley, M. F.; Koey, O. *J. Org. Chem.* **1988**, *53*, 205.

(7) Use of the allyl reagent for selective protection of unhindered carbohydrate alcohols: Harada, T.; Yamada, H.; Tsukamoto, H.; Takahashi, T. *J. Carbohydr. Res.* **1995**, *14*, 165.

(8) Dip in the curve at 7400 s is a result of removing heat by taking the TLC sample.

Scheme 1



decomposition pathway, but the ethyl derivative **6b** is more stable than **6a**. It is for this reason that very hindered alcohols fail to give carbonates with these reagents.

With this new method in hand, we explored the generality of the process. Figure 3 shows that the overall efficiency and generality of the reaction is excellent. Two of the alcohols examined, 7-TES-baccatin III **21** and the 11*β*-hydroxyl of steroid **9**, could not be derivatized because of steric hindrance, which is in contrast to the 11α-hydroxy steroids that react efficiently. Only reagent decomposition was observed. All other alcohols tested gave clean conversions to their respective carbonates.[9]

Acknowledgment. We thank Sean Lapekas for performing the ReactIR experiment and Steve L. Snyder for running the DSCs.

Supporting Information Available: Experimental procedures, NMR, and HRMS data for the preparation of **2b**, **2c**, **8**−**20**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) In general, these reactions were performed by dissolving the alcohol in 10 mL/g of pyridine and 2.5 mL/g of TEA and adding reagent **6** (2 equiv/OH group) and a catalytic amount of DMAP. When the reaction was complete as determined by TLC or heat flow, the product was isolated by extraction with EtOAc. In some of the steroid examples, isolation was performed simply by slowly adding water to crystallize the product.