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A New Method for the Conversion of Secondary and Tertiary Amides to Bridged Orthoesters.

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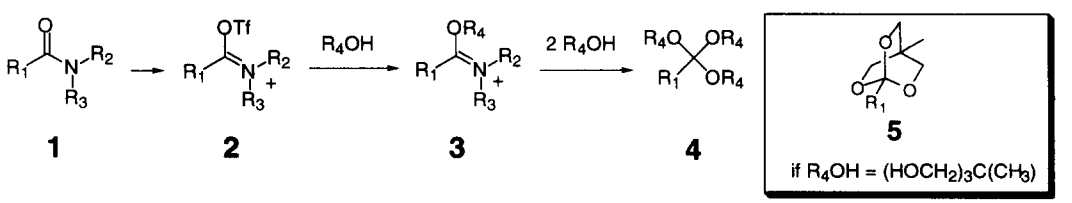
Abstract: Secondary and tertiary amides were treated with trifluoromethanesulfonic (triflic) anhydride in the presence of pyridine at low temperatures to generate imino and iminium triflates. Successive treatment with 2,2-bishydroxymethyl-1-propanol in the pyridine buffered solution gave the corresponding 2,6,7-trioxabicyclo[2.2.2]octane orthoesters in good to excellent yields at below room temperature. © 1997 Elsevier Science Ltd.

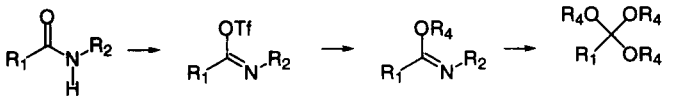
Although underused, orthoesters are one of the most useful protecting groups for carboxylic acids due to their stability towards very strong bases and their lability towards very mild acidic hydrolysis.[1,2] Bridged orthoesters are much more stable than their acyclic counterparts, thus, they are more easily handled and can be chromatographed without extensive hydrolysis. In the past, bridged orthoesters have been made by treating imidoesters[3] or another orthoester[4] with a triol. More recently, Corey has shown an elegant method of converting the carboxylic acid chlorides to 3-methyl-3-hydroxymethyloxetane esters using $BF_3 \cdot Et_2O$ to promote its rearrangement to the bridged orthoesters.[5] Herein, we describe an efficent one pot conversion of tertiary and secondary amides directly to their corresponding bridged orthoesters. This tactic allows one to convert one very useful and robust carboxylic acid derivative into another possessing different, yet equally useful properties. This method is based on the nucleophilic attack of a triol on an iminium or imino triflate which is generated by the action of triflic anhydride on the amide (Scheme 1-2).[6]

Scheme 1



1 **2** **3** **4** **5**

Scheme 2

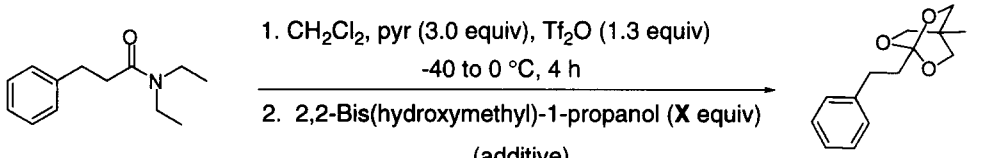


6 **7** **8** **4**

Treatment of tertiary and secondary amides with trifluoromethanesulfonic anhydride[7] at low temperatures give rise to iminium **2** and imino triflates **7**, respectively. These species are good electrophiles and they react readily with nucleophiles such as alcohols to generate the corresponding alkyl iminium ester **3** or alkyl imino ester **8** which would eventually give rise to the orthoester under mildly acidic conditions. Since acyclic orthoesters **4** are readily hydrolysed, using the readily available and inexpensive 2,2-bishydroxymethyl-1-propanol[8] should allow the more stable bridged orthoester **5** to be isolated.

In the case of these bridged orthoesters, the remaining hydroxy groups would attack the imine or the iminium carbocation in an intramolecular fashion, therefore lowering the entropic barrier for these three successive processes. Thus, using stoichiometric quantities of the triol should have been sufficient for this reaction. On the contrary, treatment of amide **9** with triflic anhydride/pyridine followed by the addition of the triol produced the desired orthoester **10** but the yield increased with the number of equivalents of the triol used (entry 1-3, Table 1). This led us to believe that the excess alcohol was also responsible for creating a more polar medium which helps in stabilizing the charged reaction intermediates. Thus, after the triol was added, the addition of acetonitrile (entry 4) or ethanol (entry 5) allowed the conversion of the amide to the bridged orthoester to occur with equal efficiency while using only a very slight excess (1.5 equiv) of the triol.

Table 1. Optimization of the conditions for orthoester formation.[a]



9 **10**

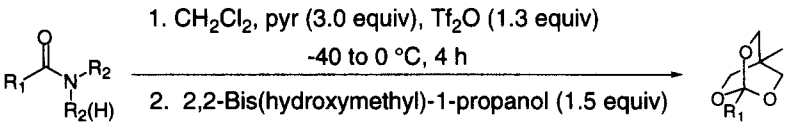
Entry	equiv of triol	Additive	Yield of **10**
1	1.5	none	58 %
2	3.5	none	83 %
3	7.0	none	86 %
4	1.5	EtOH (0.8 ml)	88 %
5	1.5	CH_3CN (2 ml)	85 %

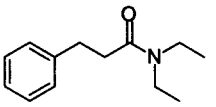
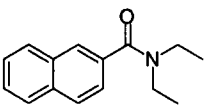
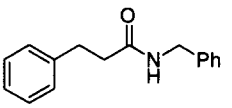
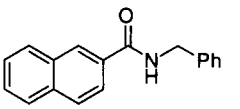
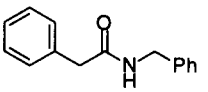
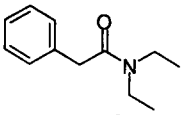
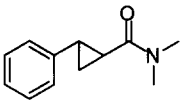
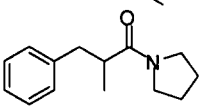
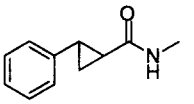
[a] Reaction was carried out on 1 mmol of substrate in 10 ml of CH_2Cl_2.

This methodology was found to be equally applicable to both secondary and tertiary amides (Table 2).[9] The only exception observed by us was that the (*E*)-*N*-methyl-3-phenylcyclopropanecarboxamide (entry 9) was readily converted to the bridged cyclic orthoester, whereas the corresponding *N*,*N*-dimethylamide (entry

8) failed to give the desired orthoester, presumably due to the sensitive nature of the phenylcyclopropane towards carbocationic ring opening. Primary amides are readily converted to nitriles upon treatment with triflic anhydride so they are not suitable substrates for this methodology. Several of these orthoesters derived from 2,2-bis(hydroxymethyl)-1-propanol were found to be crystalline solids and very non-polar relative to other components of the reaction. Thus, a work-up consisting simply of a filtration through silica gel often gave compounds which were analytically pure.

Table 2. Orthoester formation from various amides.[10]



Entry	Substrate	Yield	Entry	Substrate	Yield
1		88%	6		69%
2		76%	7		70%
3		81%			
4		72%	8		<10%
5		59%	9		67%

In conclusion, we have demonstrated that amides can be efficiently converted to bridged orthoesters using a very mild one-pot transformation.

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6 Some nucleophiles have been added to imino triflates: Azides: (a) Thomas, E. W. *Synthesis* **1993**, 767-768. Cyanides: (b) Sisti, N. J.; Fowler, F. W.; Grierson, D. S. *Synlett* **1991**, 816-818; (c) Sisti, N. J.; Zeller, E.; Grierson, D. S.; Fowler, F. W. *J. Org. Chem.* **1997**, *62*, 2093-2097.
7. Trifluoromethanesulfonic anhydride was prepared from triflic acid by the procedure of (a) Granstad, T.; Haszeldi, R. N. *J. Chem. Soc.* **1956**, 173-180; (b) Burdon, J.; Farazmaird, I.; Stacey, M.; Tatlow, J. C. *J. Chem. Soc.* **1957**, 2574-2578.
8. 2,2-Bis(hydroxymethyl)-1-propanol obtained from Aldrich and stored in vacuo with P_2O_5. Hydrated 2,2-bis(hydroxymethyl)-1-propanol could be dried by azeotropic removal of water (toluene, Dean-Stark)
9. **General procedure for the conversion of secondary and tertiary amides to bridged ortho esters:** Pyridine (3.0 equiv) was added to the amide (1 mmol) in 10 mL of anhydrous CH_2Cl_2 under an argon atmosphere. The reaction was cooled to -40 °C and trifluoromethanesulfonic anhydride was added slowly down the side of the flask into the solution. The reaction was stirred and allowed to warm up to 0 °C and stirring was continued for an additional 4 h at which time the solution would become slightly yellow or orange. The septum was then temporarily removed to allow the quick introduction of 1.5 equiv of the triol (2,2-bis(hydroxymethyl)-1-propanol). Ethanol (0.8 mL) and MeCN (2 mL) were then added via a syringe and the reaction was allowed to stir for another 6 to 12 h. The reaction was worked up by filtering through neutralized silica gel. The reaction medium was transferred using CH_2Cl_2 onto silica in a sintered glass funnel which was pretreated with 5% Et_3N in a 1:2 Et_2O-pentane mixture which also serves as the eluant. After filtering, the solvent was removed in vacuo to provide an almost analytically pure compound which could be further purified by recrystallization from hexanes-Et_2O or by flash chromatography on silica gel using 5-15% EtOAc in hexanes with 2% Et_3N.
10. All the compounds were characterized by H^1 and C^{13} NMR, IR, mp, HRMS and/or elemental analysis.

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