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Efficient and Controllably Selective Preparation of Esters Using Uronium-Based Coupling Agents

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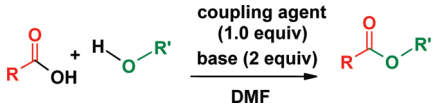
ABSTRACT



Carboxylic acid esters can be prepared in excellent yields at room temperature from an acid and either a phenol or an aliphatic alcohol using the peptide coupling reagents, TBTU, TATU, or COMU, in the presence of organic bases. Reactions using TBTU and TATU are faster but do not occur with tertiary alcohols. Selectivity between reaction with primary or secondary alcohols in diols and polyols can be achieved with choice of base and coupling agent.

A very large number of methods are available for formation of esters from carboxylic acids and alcohols.[1] When both the carboxylic acid and the alcohol are large and acid or base sensitive, fewer options are available, but these are still numerous. The methods used most commonly include dehydration with dicyclohexylcarbodiimide (DCC) and DMAP[2] or 4-(1-pyrrolidinyl)pyridine[3] and reaction with 2-halopyridinium salts[4] or sterically hindered aromatic acid anhydrides[5] or chlorides.[6] Some newer reagents include dimethylsulfamoyl chloride,[7] triphenylphosphine dihalides,[8] 1-tosylimidazole,[9] and *O*-alkylisoureas.[10] We wanted conditions for ester formation that could be used for the efficient convergent synthesis of polyester dendrimers under very mild conditions.[11] The ester groups present in both the divergently assembled polyalcoholic core and the carboxylic acid-terminated dendron ruled out transesterification conditions and either strong Brønsted or Lewis acids or bases. Agents for formation of amides from amino acids under conditions that are mild enough that racemization is minimized[12] meet these requirements. Many of these reagents are commercially available compounds that are stable in air at room temperature. They are very effective at promoting amide formation at room temperature, but only scattered

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reports[13] have appeared about their application to ester formation and those concerned formation of phenolic esters[13a] and primary aliphatic esters[13] using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium salts (TBTU and HBTU). An alternative approach employed only with primary alcohols is to use the uronium salt precursor, 1-hydroxybenzotriazole, with DCC and DMAP.[14]

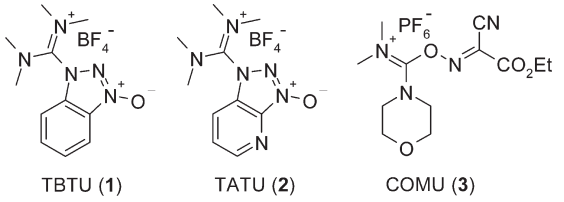

Figure 1. Structures of the uronium-based coupling agents used.

Here, we report that uronium-based peptide coupling agents, namely, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (**1**),[12a] 2-(1*H*-7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU) (**2**),[12b] and 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylaminomorpholinomethylene)]methanaminium hexafluorophosphate (COMU) (**3**),[12d] depicted in Figure 1 and commercially available, are efficient reagents for the promotion of ester formation at room temperature.

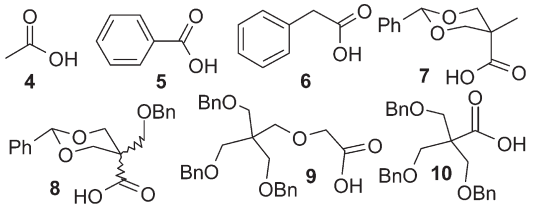

Figure 2. Structures of the carboxylic acids used.

The acids and alcohols used in this study are shown in Figures 2 and 3. Most are known compounds; compound **9** was made from tri-*O*-benzylpentaerythritol[11,15] (see the Supporting Information).

Reactions were initially performed in anhydrous DMF using equivalent amounts of acid and alcohol at room temperature with 2 equiv of base. Table 1 shows the results

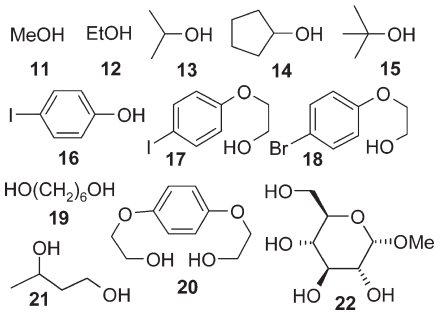

Figure 3. Structures of the alcohols used.

obtained under these conditions, with the yields given being of isolated products. The reactions worked equally well in acetonitrile but were much slower in tetrahydrofuran. In DMF, ester formation with phenols occurred rapidly and in good yields with all three coupling agents. With a variety of primary alcohols, ester formation was again very efficient, if somewhat slower. With secondary alcohols, reactions took about 4 h to complete with the benzotriazole-derived coupling agents, TATU and TBTU, but were 5−10 times slower with COMU. Reactions with *tert*-butyl alcohol were achieved with COMU in good yield, but only when the stronger[16] base, 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (MTBD), was used. The use of MTDB did not appear to significantly accelerate the COMU-promoted reaction of benzoic acid and isopropanol. TATU and TBTU did not promote esterification with tertiary alcohols.

Several other differences were noticed between the reactions performed with COMU as opposed to those with TATU and TBTU. The two latter reagents required a ~30 min activation time of the acid by the coupling agent before the alcohol was added. COMU did not require an activation time. With COMU, it did not matter whether diisopropylethylamine (DIEA) or the stronger[16] base, DBU, was used for phenols or primary or secondary alcohols. However, with TBTU and TATU, secondary alcohols did not react when DIEA was used as the base.

Yields were observed to be lower for secondary alcohols when equimolar amounts of acid, alcohol and coupling agent were used. Using 1.2 equiv of acid and 1.5 equiv of coupling agent increased the yield of esterification of benzoic acid with cyclopentanol using COMU from 68% in 16 h to 81% in 10 h. Similarly, esterification of benzoic acid with isopropyl alcohol and TBTU under these conditions gave a yield of 91%, as opposed to 63% under equimolar conditions.

An evaluation of whether the base sensitivity of reaction outcome to alcohol structure could be used to obtain regioselectivity was tested with a diol (**21**) and a polyol

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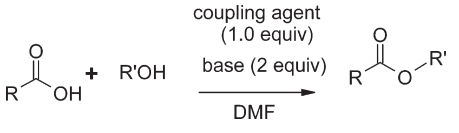
Table 1. Reactions of Carboxylic Acids and Alcohols at Room Temperature



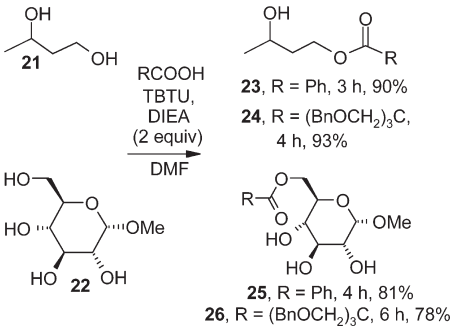
acid	alcohol	coupling agent[a]	base[b]	time (h)	yield[c] (%)
5	**16**	TBTU	DIEA	0.25	86
	16	TATU	DIEA	0.25	96
	16	COMU	DIEA	3	79
	12	COMU	DBU	2.5	89
	17	TBTU	DBU	0.5	81
	17	TATU	DIEA	0.5	95
	17	COMU	DBU	4.5	74
	20	COMU	DBU	5	69
	13	TBTU	DBU	4	63
	13	COMU	DBU	16	71
	13	COMU	MTBD	11	79
	14	TBTU	DBU	4	59
	14	TATU	DBU	3.5	89
	14	COMU	DBU	16	68
	15	TBTU	DBU	36	0
	15	TATU	DBU	36	0
	15	COMU	DBU	36	0
	15	TATU	MTBD	36	0
	15	COMU	MTBD	16	79
4	**17**	COMU	DBU	2	86
6	**16**	COMU	DBU	3	81
6	**19**	COMU	DBU	4	83
6	**20**	COMU	DBU	4	67
7	**18**	TBTU	DBU	1	72
7	**17**	COMU	DBU	12	73
8	**17**	TBTU	DBU	3	60
8	**17**	COMU	DBU	14	62
9	**11**	COMU	DBU	2	81

[a] Reactions with TATU were conducted with 1.2 equiv of the acid and 1.3 equiv of TATU. [b] Abbreviations: DIEA, diisopropylethylamine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; MTBD, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene. [c] Isolated yields.

(**22**) using TBTU and DIEA with an aryl (**5**) and an aliphatic acid (**10**). The reactions were highly selective for the primary hydroxyls; in only one reaction was a small amount of the secondary product obtained, that is for 1,3-butanediol (**21**) (see Scheme 1), where benzoylation gave 5% of the secondary product in addition to the major primary product (90%). Most other selective esterification methods[17] are less selective in benzoylation of **21** than this method.

Mechanisms have been proposed for the reactions involving COMU and amines[18] and for TBTU and alcohols (see Scheme 2).[13a] These mechanisms have the following

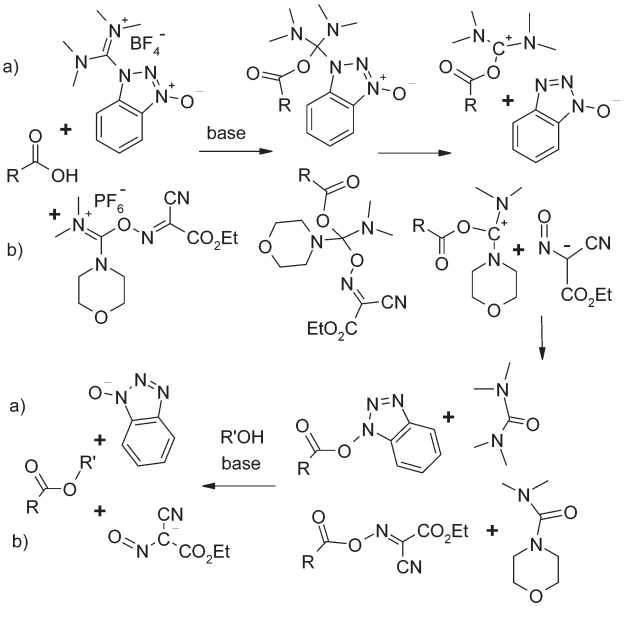
Scheme 1. Selective Esterifications[a]



[a] Note that **23** was accompanied by 5% of the ester of the secondary alcohol.

steps: addition of the carboxylate salt to the uronium reagent, decomposition of the resulting tetrahedral intermediate, addition of the released anion to the carbonyl center followed by loss of a urea derivative, and alcohol addition to the activated carbonyl group. The base sensitivity of the reaction with secondary alcohols performed with the benzotriazole-derived coupling agents indicates that the last step is rate determining in this case. Conversely, for the slower base-insensitive COMU reactions, an earlier step must be rate determining for primary and secondary alcohols, either the decomposition of the initial tetrahedral intermediate or the readdition of the stable anion. However, with the tertiary alcohol, *tert*-butyl alcohol, ester formation only occurs with the strong organic base MTBD using COMU. Clearly, the rate-determining step for COMU has switched to being the last step for this hindered alcohol. The relative acidities in DMSO and

Scheme 2. Proposed Reaction Mechanisms: (a) Level on Each Line, TBTU Mechanism; (b) Level, COMU Mechanism



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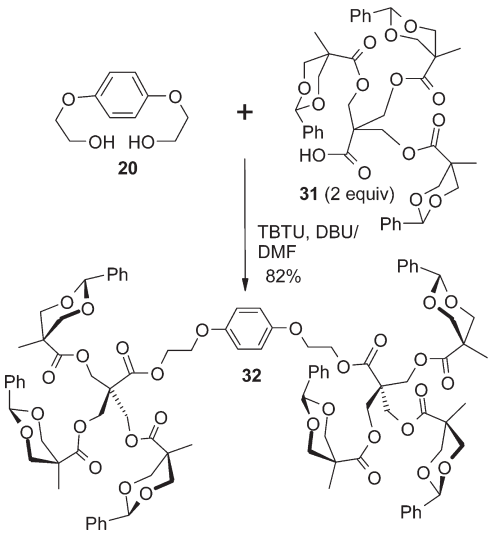
Scheme 3. TBTU-Promoted Convergent Synthesis of a Second-Generation Dendrimer[a]



[a] The synthesis of the second-generation dendron **31** is outlined in the Supporting Information.

acetonitrile of alcohols and the conjugate acids of the organic bases employed[16,19] indicate that the alcohol will only be slightly ionized. The difference in pK_a between isopropyl alcohol and *tert*-butyl alcohol[19a] is similar to that between DBU and MTBD.[16] It appears that the tetrahedral intermediate for alcohol addition is lower in energy relative to starting materials for COMU than for the benzotriazole-derived coupling agents, for either electronic or steric reasons.

Having established that these conditions were effective for ester formation, we tested whether they could be used for the convergent synthesis of polyester dendrimers. Diol **20** is a dendrimer core molecule that we recently prepared.[11] We have shown that tribranched dendrons can be added to core **20** to form ester linkages if the carboxylic acid of the dendron is preactivated as the anhydride.[11] In Scheme 3, we show that peptide coupling agents can also be used for this purpose, forming the two ester linkages of **32** in good yield under mild conditions. This approach eliminates one chemical step during the creation of each generation of a polyester dendrimer. The formation of other esters from acid **31** and simple alcohols as well as the synthesis of the tribranched second generation dendron **31** is described in the Supporting Information.

In summary, we have demonstrated that the peptide coupling reagents COMU, TBTU, and TATU can be used to prepare esters in excellent yields from all types of alcohols at room temperature under mild conditions using organic bases and short reaction times. Esterification of secondary alcohols promoted by TBTU and TATU require a base, such as DBU, that is stronger than tertiary amines. Only COMU is effective for the preparation of esters from tertiary alcohols, and then only when the still stronger base, MTBD, is used. The base sensitivity of the TBTU and TATU promoted reactions can be utilized for the selective esterification of primary hydroxyls in diols and polyols. Applications of this latter observation will be reported shortly.

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Supporting Information Available. Experimental procedures for all syntheses, characterization data of new compounds, and ^{1}H and ^{13}C NMR spectra for all compounds prepared. This information is available free of charge via the Internet at http://pubs.acs.org.

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