ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Selective Esterifications of Primary Alcohols in a Water-Containing Solvent

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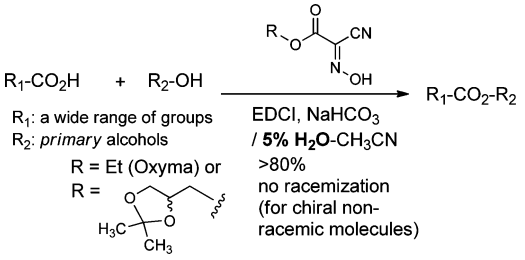
Received August 13, 2012

ABSTRACT



Oxyma and an oxyma derivative, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-cyano-2-(hydroxyimino)acetate (5b), displayed a remarkable effect on selective esterifications of *primary* alcohols. A wide range of carboxylic acids could be esterified with *primary* alcohols by using EDCI, $NaHCO_3$, and Oxyma or Oxyma derivative 5b in 5% H_2O–CH_3CN. Oxyma derivative 5b is particularly useful, since it could be removed after the reaction via a simple basic or an acidic aqueous workup procedure.

In our efforts towards the total synthesis of muraymycins A_1 (**1**) and D_1 (**2**), and their analogs for structure–activity relationship studies against Gram-positive bacteria including *M. tuberculosis*, it is crucial to develop an efficient synthesis of the dipeptide **3a** and **3b** (Figure 1).[1] We have recently reported an efficient synthesis of the ureidomuraymycidine derivatives (the partial structure highlighted in a box in Figure 1).[1b] In the synthesis of muraymycin A_1 selective acetylation of the *primary* alcohol is necessary to accomplish an efficient synthesis of the left half of **1**. We have screened reported esterification conditions for **4a** to form the monoacetate **3a**. Although several acetylation conditions with the controlled amounts of reagents and at lowered temperatures provided the monoacetate at the *primary* alcohol, the selectivity of mono- and diacetate was not satisfactory. For example, acetylation of **4a** with Ac_2O (5 equiv) and pyridine (10 equiv) in CH_2Cl_2 at 0 °C gave a mixture of **3a** and the diacetate (3/1) in less than 40% yield. DCC-mediated acetylations under anhydrous conditions yielded the diacetate as a major product. Thus, we commenced optimizing esterification conditions that protect the *primary* alcohol of **4a** with AcOH to yield **3a** exclusively.

In our recent finding of amide-forming reactions with the ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma formerly known as EACNOx)[2] derivative (glyceroacetonide-Oxyma, **5b** in Table 1) in water media, it was observed that the **5b**-esters of amino acids (e.g., **9**) are stable during amide-forming reactions in water. Typically, glyceroacetonide-Oxyma catalyzed amide-forming reactions could be achieved with EDCI (1.5 equiv), $NaHCO_3$ (3–6 equiv) in water (0.2–0.3 M) to yield the corresponding peptides in greater than 90% yield without detectable diastereomers.[3] It has been reported that nucleophilicity of the oxygen atom of alcohols is slightly stronger than that of water.[4] Thus, we expected that selective coupling of the oxime-esters **9** (Table 1) with alcohols could be achieved in water

(1) (a) Kurosu, M.; Li, K. *J. Org. Chem.* **2008**, *73*, 9767–9770. (b) Aleiwi, B. A.; Schneider, C. M.; Kurosu, M. *J. Org. Chem.* **2012**, *77*, 3859–3867. (c) Aleiwi, B. A.; Kurosu, M. *Tetrahedron Lett.* **2012**, *53*, 3758–3762.

(2) (a) Khattab, S. N. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1374–1379. (b) El-Faham, A.; Subiro's-Funosas, R.; Albericio, F. *Chem.—Eur. J.* **2010**, *19*, 3641–3649. (c) Subiro's-Funosas, R.; Prohens, R.; Barbas, R.; El-Faham, A.; Albericio, F. *Chem.—Eur. J.* **2009**, *15*, 9394–9403. (d) Thouin, E.; Lubell, W. D. *Tetrahedron Lett.* **2000**, *41*, 457–460. (e) Kaiser, E. T.; Mihara, H.; Laforet, G. A.; Kelly, J. W.; Walters, L.; Findeis, M. A.; Sasaki, T. *Science* **1989**, *243*, 187–192.

(3) Wang, Q.; Wang, Y.; Kurosu, M. *Org. Lett.* **2012**, *14*, 3372–3375.

(4) (a) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827–1836. (b) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319–326.

10.1021/ol3022337

media in the presence of a weak base. Gratifyingly, acetylation of **4a** with excess AcOH (10 equiv), glyceroacetonide-Oxyma **5b** (5 equiv), and $NaHCO_3$ (10 equiv) in water (0.2 M) provided the monoacetate **3a** in 85% yield without the formation of the diacetate (R_2 = OAc in **3a** in Figure 1). Herein, we report the optimization of selective esterifications of *primary* alcohols with Oxyma **5a** or glyceroacetonide-Oxyma **5b**, EDCI, and $NaHCO_3$ in water-containing solvent systems.

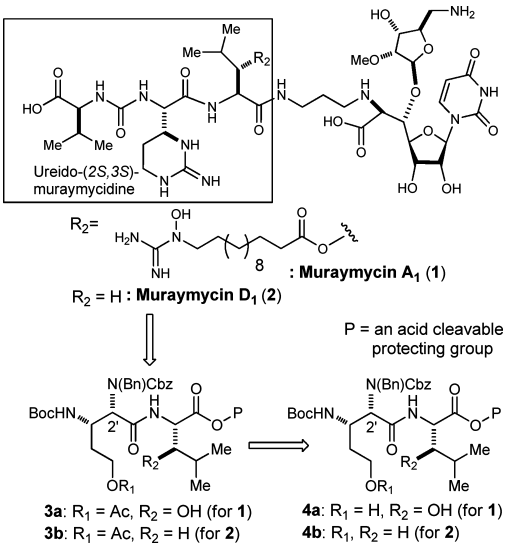
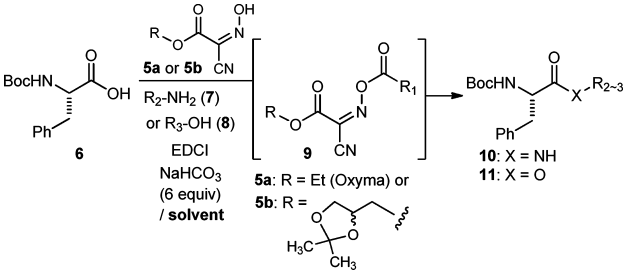


Figure 1. Syntheses of muraymycins A_1 (**1**) and D_1 (**2**).

Although an acetylation of **4a** to form **3a** could be achieved in water with excess reagents, high-yielding esterifications of alcohols using a limited amount of carboxylic acids or alcohols are considered to be challenging transformations in aqueous media. Uronium-based reagents have previously been applied to introduce esters on *primary* alcohols under nonaqueous conditions.[5] To the best of our knowledge, no practical esterification reaction has been developed in water-containing solvent systems. We have observed that glyceroacetonide-Oxyma **5b** is beneficial in high-yielding amide-forming reactions in water with a wide range of amino acid derivatives.[3] The reactivity difference between Oxyma **5a** and **5b** in amide-forming reactions in water is attributed to the fact that the water solubility of **5b** is improved 2.1 times greater than that of **5a** at pH 8.3 (entries 1 and 2 in Table 1).[6] The esterification reactions of Boc-L-Phe-OH (**6**, 1 equiv) with alcohols (2 equiv), **5a** or **5b** (1.5 equiv), EDCI (1.5 equiv), and $NaHCO_3$ (6 equiv) were examined in water and water-containing solvent systems, and these data are summarized in Table 1. Esterification of **6** with MeOH in water furnished Boc-L-Phe-OMe (**11a**) in 45% yield in 2 h (entry 3). This low-yielding reaction in entry 3 was attributed to a slower reaction rate of the esterification compared to the amide-forming reaction in entry 1. In addition, it was realized that the oxime-ester intermediate **9** has a half-life of approximately 6 h in water at pH 8.3.[7] Thus, we examined the effect of a cosolvent to increase the nucleophilicity of alcohol and the half-life of **9**. The same reaction in H_2O-CH_3CN (1/1) improved the isolated yield of **11a** to 55% after 2 h (entry 4). Significant improvement in the methyl esterification of **6** was observed when the reaction was performed in 5% H_2O-CH_3CN (entry 5); the isolated yield of **11a** was greater than 95%. Oxyma **5a** could effectively serve as a coupling additive for an esterification reaction in the solvent system (5% H_2O-CH_3CN) (entry 6). Thus, further studies of selective esterifications of *primary* alcohols were

Table 1. Amide- or Ester-Forming Reactions in Water Media



entry	additive/ solvent	7 or 8	product (10 or 11)	yield (%)[d]
1[a]	**5b** H_2O	HCl•H-L-Ala-OMe (**7a**)	Boc-Phe-Ala-OMe (**10a**)[c]	93
2[a]	**5a** H_2O	**7a**	**10a**[c]	25
3[b]	**5b** H_2O	MeOH	Boc-Phe-OMe (**11a**)[c]	45
4[b]	**5b** 50% H_2O-CH_3CN	MeOH	**11a**	55
5[b]	**5b** 5% H_2O-CH_3CN	MeOH	**11a**[c]	>95
6[b]	**5a** 5% H_2O-CH_3CN	MeOH	**11a**[c]	>95
7[b]	**5a** 5% H_2O-dioxane	MeOH	**11a**[c]	90
8[b]	**5a** 5% H_2O-acetone	MeOH	**11a**[c]	85
9[b]	**5a** 5% H_2O-CH_3CN	^{i}PrOH	Boc-Phe-O^{i}Pr (**11b**)[c]	0
10[b]	**5a** 5% H_2O-CH_3CN	^{t}BuOH	Boc-Phe-O^{t}Bu (**11c**)[c]	0

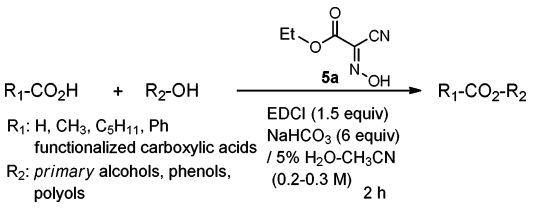
[a] **6** (1.0 equiv), **7** (1.5 equiv), additive (1.5 equiv), EDCI (1.5 equiv), $NaHCO_3$ (6 equiv) in H_2O (0.2 M concentrations), 2 h. [b] **6** (1.0 equiv), **8** (2.0 equiv), additive (1.5 equiv), EDCI (1.5 equiv), $NaHCO_3$ (6 equiv) (0.2 M concentrations). [c] *de* or *ee* was determined to be > 99% via HPLC analysis. [d] Isolated yield.

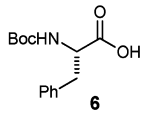
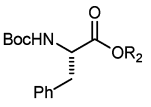
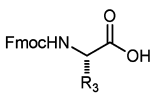
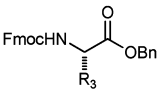
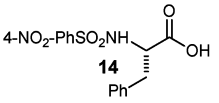
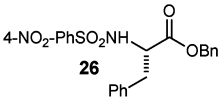
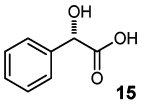
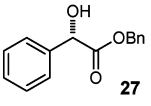
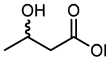
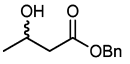
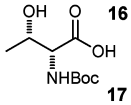
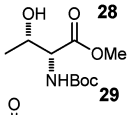
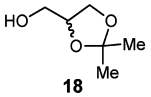
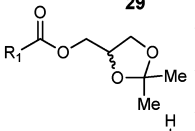
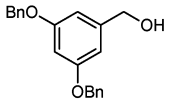
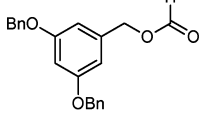
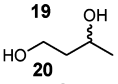
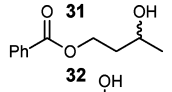
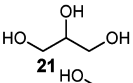
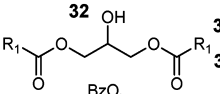
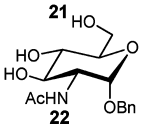
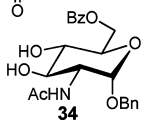
(5) (a) Twibanire, J. K.; Grindley, T. B. *Org. Lett.* **2011**, *13*, 2988–2991. (b) Twibanire, J. K.; Omran, R. P.; Grindley, T. B. *Org. Lett.* **2012**, *14*, 3909–3911.

(6) 6 equiv of $NaHCO_3$ in water (0.2 M) shows pH of 8.3.

(7) The acetate and benzoate of **5b** have a half-life of over 12 h.

Table 2. Selective Esterifications of *Primary* Alcohols Using EDCI, Oxyma **5a**, and $NaHCO_3$ in 5% H_2O-CH_3CN[a]

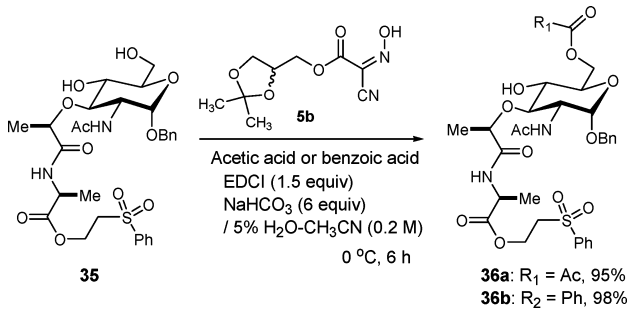


entry	R_1-CO_2H	R_2-OH	product	yield (%)	*ee* (%)[b]
1[c]	 **6**	EtOH	 **23a**: R_2 = Et	95	>99
2[c]		*n*-hexanol	**23b**: R_2 = C_6H_{13}	97	>99
3[c]		allyl alcohol	**23c**: R_2 = allyl	98	>99
4[c]		BnOH	**23d**: R_2 = Bn	99	>99
5[c]		Phenol	**23e**: R_2 = Ph	95	>99
6[c]		4-chlorophenol	**23f**: R_2 = 4-Cl-Ph	95	>99
7[c]		2,4,6-trichlorophenol	**23g**: R_2 = 2,3,4-tri-Cl-Ph	90	-
8[c]	 **12**: R_3 = 4-(OH) $PhCH_2$	BnOH[g]	 **24**: R_3 = 4-(OH) $PhCH_2$	96	>99
9[c]	**13**: R_3 = ^{i}Pr	BnOH	**25**: R_3 = ^{i}Pr	95	>99
10[c]	 **14**	BnOH	 **26**	98	>99
11[c]	 **15**	BnOH	 **27**	98	>99
12[c]	 **16**	BnOH	 **28**	99	-
13[c]	 **17**	MeOH	 **29**	95	>99
14[d]	R_1 = Ph	 **18**	 **30a**: R_1 = Ph	>95	-
15[d]	R_1 = CH_3		**30b**: R_1 = CH_3	99	-
16[d]	R_1 = H		**30c**: R_1 = H	>95[e]	-
17[d]	R_1 = H	 **19**		95	-
18[d]	R_1 = Ph	 **20**	 **31**	80	-
19[d]	R_1 = Ph	 **21**	 **32** **33a**: R_1 = Ph	85	-
20[d]	R_1 = C_5H_{11}		**33b**: R_1 = C_5H_{11}	90	-
21[d,f]	R_1 = Ph	 **22**	 **34**	90	-

[a] All reactions were carried out using **5a** (1.5 equiv) at rt except where noted. [b] *ee* was determined by HPLC (Daicel Chiralcel OD-H column). [c] R_1-CO_2H (1 equiv) and R_2-OH (2 equiv) were used. [d] R_1-CO_2H (2 equiv) and R_2-OH (1 equiv) were used. [e] Yield was determined *via* ^{1}H NMR. [f] The reaction was carried out at 0 °C. [g] R_1-CO_2H (1 equiv) and R_2-OH (8 equiv) were used.

performed using Oxyma **5a**. Although several solvents such as 5% H_2O–dioxane and 5% H_2O–acetone could be utilized for effective methyl esterification of **6** (entries 7 and 8), the esterifications in 5% H_2O-CH_3CN were

Scheme 1. Selective Acylations of **35**



superior to those in the other solvent systems tested. Under the optimized conditions [acid (1 equiv), alcohol (2 equiv), **5a** or **5b** (1.5 equiv), EDCI (1.5 equiv), and $NaHCO_3$ (6 equiv)], isopropanol and *tert*-butanol did not form the corresponding esters with **6** even after a prolonged reaction time.[8]

In order to understand the scope and limitations of the selective esterification reactions of *primary* alcohols with EDCI, Oxyma **5a**, and $NaHCO_3$ in 5% H_2O-CH_3CN, these conditions were applied to esterifications of a wide variety of acids with alcohols. Selected examples are summarized in Table 2. Esterifications of **6** with methanol, *primary* alcohols, and phenols furnished the corresponding esters in greater than 90% yield without detectable racemization (entries 1−7). Significantly, an allyl alcohol could be esterified to provide **23c** in 98% yield. It is worth pointing out that esterifications of carboxylic acid with allyl alcohols have never been successfully performed using carbodiimide-mediated reaction conditions (entry 3).[9] Unlike 4-(dialkylamino)pyridine-catalyzed DCC-mediated esterification conditions, the Fmoc-group was not cleaved during the benzyl esterifications of the Fmoc-protected amino acids, **12** and **13** (entries 8 and 9).[10] Esterifications of *N*-sulfonylated α-amino acids using carbodiimide coupling reagents often result in low conversion with significant racemization. However, under the conditions in Table 2, the benzyl esterification of **14** furnished **26** in 98% yield with >99% *ee* (entry 10). The chiral carboxylic acids possessing *secondary* alcohols, **15**, **16**, and **17**, could be esterified efficiently with the *primary* alcohols. Benzyl esterifications of (*S*)-mandelic acid (**15**) and 3-hydroxybutanoic acid (**16**) furnished the corresponding benzyl esters **27** and **28** in 98% and 99% yields, respectively (entries 11 and 12). Methyl esterification of Boc-L-Thr-OH (**17**) gave rise to Boc-L-Thr-OMe (**29**) in 95% yield (entry 13). Benzoylation, acetylation, and formylation reactions of DL-1,2-isopropylideneglycerol (**18**) provided the corresponding esters **30a**−**c** in greater than 95% yields (entries 14−16). It should be noted that (2,2-dimethyl-1,3-dioxolan-4-yl)methyl formate (**30c**) was not stable to silica gel; thus, its yield was determined based on ^1H NMR analysis of the crude product. On the other hand, formylation of (3,5-bis(benzyloxy)phenyl)methanol (**19**) afforded **31** in 95% yield after silica gel chromatography (entry 17). Selective esterifications of diols were also demonstrated, and selected examples are summarized in Table 2. The *primary* alcohol of butane-1,3-diol (**20**) was selectively benzoylated to afford **32** in 80% yield. Esterifications of glycerol (**21**) with benzoic acid and *n*-hexanoic acid furnished the corresponding diesters **33a** and **33b** in 85% and 90% yield, respectively (entries 19 and 20). Benzoylation of benzyl 2-(acetylamino)-2-deoxy-α-D-glucopyranoside (**22**) was achieved selectively at the C6-position to afford the monobenzoate **34** in 90% yield (entry 21).

Finally, acylations of the diol of a complex muramic acid derivative **35** were demonstrated as selective esterifications of *primary* alcohols (Scheme 1).[11] Acetylation and benzoylation of **35** using **5b** (1.5 equiv), acid (2 equiv), EDCI (1.5 equiv), and $NaHCO_3$ (6 equiv) at 0 °C gave rise to the *primary* acetate **36a** and benzoate **36b** in greater than 95% yield without the formation of diacylated products. In the reactions summarized in Scheme 1, it is a significant benefit to use glyceroacetonide-Oxyma **5b**. Although the same reaction with Oxyma **5a** gave an equal conversion yield as observed in Scheme 1, separation of **5a** from the product was extremely difficult via silica gel chromatography. On the other hand, **5b** could be removed completely via standard acidic and basic workups.

In conclusion, we have optimized selective esterifications of *primary* alcohols using Oxyma **5a** or glyceroacetonide-Oxyma **5b**, EDCI, and $NaHCO_3$ in 5% H_2O-CH_3CN. The selective esterification conditions described here do not require the strict anhydrous conditions necessary for ordinal esterification reactions. The coupling additive **5b** can be removed easily after the reactions via acidic and basic workups. The new esterification conditions reported here should be a valuable asset in organic synthesis and for selective modifications of polyol molecules.

Acknowledgment. We thank the National Institutes of Health (NIAID Grant AI AI084411) and University of Tennessee for generous financial support.

Supporting Information Available. Experimental procedures and copies of NMRs. This is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(8) Esterifications of **6** with (+)-menthol and cholesterol also did not provide the corresponding esters.

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(11) Under the optimized conditions, acetylation of **4a** furnished **3a** in greater than 95% yield without the formation of the diacetate (Figure 1).