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Nonmetal Catalyzed Insertion Reactions of Diazocarbonyls to Acid Derivatives in Fluorinated Alcohols

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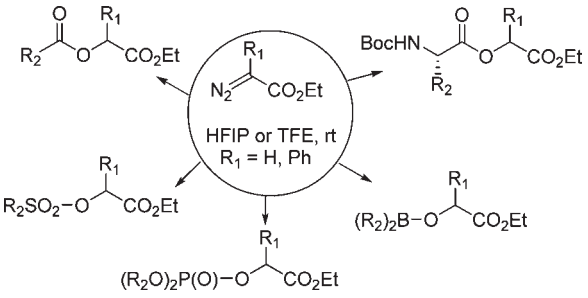
ABSTRACT



The insertion reaction of diazocarbonyls to acids could be performed smoothly in fluorinated alcohols in the absence of metal catalyst. This new procedure allowed the chemoselective preparation of various functionalized compounds such as acyloxyesters, depsipeptides, and sulfonate, phosphonate, or boronate derivatives.

α-Acyloxy carbonyls are found as structural units in many natural products and are also useful synthetic building blocks. Among them depsipeptides are interesting classes of biopolymers (Figure 1). They show various biological activities with antibacterial, antiviral, antifungal, and anti-inflammatory properties,[1] and some of them are also efficient in cancer treatment.[2] α-Acyloxy ester motifs are obtained by several methods, generally by treatment of acids with α-hydroxy,[3] α-halogeno carbonyls[4] or via the Passerini reaction.[5] Another alternative method which is less developed is the reaction of carboxylic acids with diazocarbonyl compounds. However, the latter are poorly reactive and harsh conditions are required: a large excess of carboxylic acid used as solvent, high temperature, and long reaction times.[6,7] A few examples of insertion into carboxylic acids under metal catalysis are

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(6) (a) Smith, A. B., III; Dieter, R. K. *Tetrahedron* **1981**, *37*, 2407. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (c) Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811.

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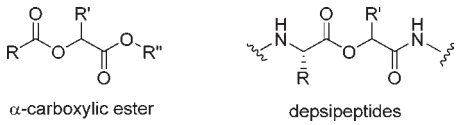


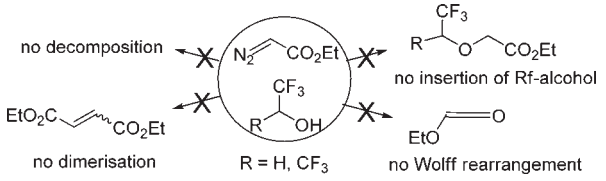
Figure 1. α-Acyloxy carbonyl motifs.

reported.[8] However reactions required protection/deprotection steps.

We report here a straightforward method which specifically introduces acids on diazocarbonyl compounds by using fluoroalkyl alcohols as solvents.

The specific physicochemical properties of fluorinated alcohols as solvents (hexafluoro-2-propanol, HFIP; trifluoroethanol, TFE) allowed us to facilitate many classical reactions and to improve yields under mild conditions.[9] Their high ability to donate a hydrogen bond and their strong ionizing power allow for avoiding Lewis acid or metal catalysis.[9] Furthermore these fluoro alcohols facilitate reactions involving poor nucleophiles.[10] For example in HFIP as solvent, carboxylic acids can act as nucleophiles for oxirane ring-opening reactions.[11]

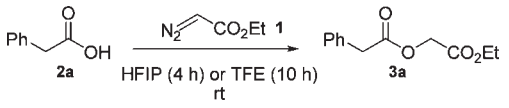
Scheme 1. Stability of the Ethyl Diazoacetate **1**



First the reactivity and the stability of the ethyl diazoacetate (EDA) **1** was evaluated in fluorinated alcohols (TFE and HFIP). As a matter of fact, diazocompounds are known to easily dimerize. Moreover, TFE and HFIP could also behave as reagents and undergo insertion. Compound **1** was solubilized either in HFIP or in TFE. Whatever the conditions, at room temperature or at reflux, no decomposition, no dimerization, and no Wolff rearrangement occurred (Scheme 1).[6,7] In addition, fluorinated alcohols were unreactive toward the diazocompound and no insertion occurred even after one day. The diazo compound was completely recovered.

We thus could investigate the reactivity of the system fluorinated alcohol/diazoacetate with carboxylic acids. When 1 equiv of $BnCO_2H$ **2a** was added to the diazoacetate in HFIP or TFE, a reaction occurred to afford, after 4 and 10 h respectively, a single product **3a** which corresponds to the acid insertion on the diazo (Scheme 2). The reaction is completely chemoselective. After distillation of the solvent and purification, the product **3a** was obtained in good yield (80% (HFIP), 77% (TFE)). Interestingly, when the reaction was performed in other solvents (diethyl ether, dichloromethane, ethanol), no reaction occurred at room temperature, and some traces of product appeared at reflux after one day in ethanol. This revealed the unique role of fluoro alcohols in the promotion of the reaction.

Scheme 2. Insertion Reaction of **1** with Acid **2a**



The reaction could be generalized to a wide range of carboxylic acids (Table 1). Alkyl and aryl acids led to the corresponding acetoxy esters (Table 1, entries 1−2). Functionalized acids having hydroxyl groups and double bonds reacted easily to afford the acetoxy acetate (Table 1, entries 3−7). This clearly demonstrates that the insertion of diazo into alcohol and a double bond is not a competitive process under these mild conditions. Another advantage of these conditions is the compatibility with sensitive protective groups. The insertion reaction with **1** and amino acids protected with a Boc or an acyl group on the nitrogen resulted in the formation of protected products **3i**−**3k** in very good yields (entries 9−11). The reaction with functionalized amino acids was again chemoselective with no insertion of the hydroxyl or the thiol observed (entries 12−13). Furthermore conditions are smooth avoiding any epimerization of the amino acids. It is worth noting that the reaction is as efficient in TFE as in HFIP albeit with a longer reaction time in some cases. Consequently this procedure allowed the easy and efficient access to depsipeptides under particularly mild conditions.

In order to study the scope of the reaction, we investigated the reaction with the disubstituted diazocarbonyl derivative **4**[12] (Table 1, entries 14−16). With all acids, the reaction efficiently afforded corresponding acyloxyesters in excellent yields. With amino acids, corresponding products were obtained in very good yields as a 1/1 mixture of diastereomers.

In the polar OH insertion reactions, three mechanisms are generally postulated (Scheme 3):[6c,13] (*a*) a protonation

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(12) Yu, W. Y.; Tsoi, Y. T; Zhou, Z. Y.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 469.

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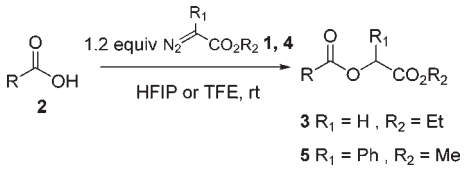
Table 1. Carboxylic Acids Insertions of Diazoacetates **1**, **4**[a]



Entry	Acid **2**	Solvent	Time (h)	Product **3-5**	Yield (%)
1	**2a**	HFIP	4	**3a**	80
		TFE	10		77
2	**2b**	HFIP	4	**3b**	85
		TFE	6		82
3	**2c**	HFIP	3.5	**3c**	94
		TFE	18		90
4	**2d**	HFIP	16	**3d**	91
		TFE	16		65
5	**2e**	HFIP	16	**3e**	86
		TFE	24		84
6	**2f**	HFIP	4	**3f**	86
		TFE	4		81
7	**2g**	HFIP	16	**3g**	86
		TFE	20		84
8	**2h**	HFIP	16	**3h**	96
		TFE	16		90
9	**2i**	HFIP	16	**3i**	75
		TFE	20		77
10	**2j**	HFIP	2	**3j**	73
		TFE	2		85
11	**2k**	HFIP	4.5	**3k**	80
		TFE	6.5		80
12	**2l**	HFIP	4.5	**3l**	90
		TFE	7		88
13	**2m**	HFIP	11	**3m**	87
		TFE	12		85
14	**2a**	HFIP	3.5	**5a**	98
		TFE	4.5		92
15	**2i**	HFIP	4.5	**5i**	98
		TFE	4.5		97
16	**2n**	HFIP	3	**5n**	89
		TFE	4		88

[a] 2.2 equiv of **1**.

of the diazo compound to give a diazonium ion which then loses nitrogen; (*b*) a nucleophilic attack on the electrophilic carbene to give an ylide, followed by hydrogen transfer; and (*c*) a concerted insertion.

Since diazocompounds are stable in fluorinated alcohols, pathways involving a previous departure of nitrogen are unlikely. Consequently it is reasonable to assume that the mechanism *via* the pathway *a* is more acceptable. The fluorous alcohol through its excellent hydrogen bond donor ability and its high ionizing power would be expected to reinforce the acidity of the carboxylic acid, thus favoring the protonation of

Scheme 3. Mechanism Postulated

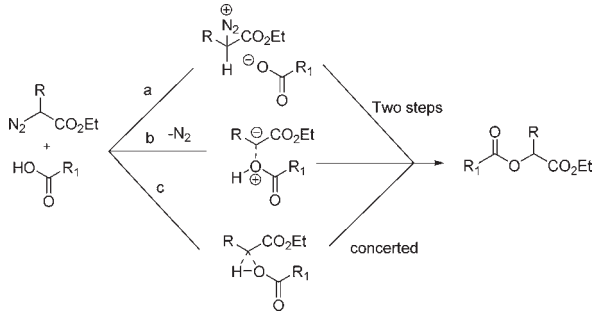


Table 2. Acid Reaction Insertion of Diazo Compounds **1**, **4**

Entry	Acids **6-10**	R_1	Solvent	Time (h)	Product **11-17**	Yield %
1[a]	PTSA **6**	H	HFIP	0.1	**11**	91
			TFE	0.1		87
2[b]	H_3PO_4 **7**	H	HFIP	0.1	**12**	76
			TFE	0.1		72
3[a]	**8**	H	HFIP	0.5	**13**	94
			TFE	10		76
4[b]	$B(OH)_3$ **9**	H	HFIP	1	**14**	85
			TFE	2		78
5[c]	$PhB(OH)_2$ **10**	H	HFIP	3	**15**	91
			TFE	4		82
6[a]	**6**	Ph	HFIP	0.3	**16**	81
			TFE	0.5		74
7[a]	**8**	Ph	HFIP	0.3	**17**	90
			TFE	0.4		84

[a] 1.2 equiv of **1** or **4**. [b] 3.3 equiv of **1** or **4**. [c] 2.2 equiv of **1** or **4**.

the diazo, followed by the displacement of nitrogen by a carboxylate.

These excellent results prompted us to extend the reaction to noncarboxylic acids. Indeed there are few reports of the insertion of sulfonic[14] and phosphonic[15] acids, and to our knowledge, no example is reported with boronic acids. These various acidic compounds could then be involved in the system HFIP/diazo compound leading to sulfonate, phosphate, and boronate derivatives, respectively, in good yields (Table 2).

(14) For sulfonic acids: (a) Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109. (b) Collins, J. C.; Dilworth, B. M.; Garvey, N. T.; Kennedy, M.; McKervey, M. A.; O'Sullivan, M. B. *J. Chem. Soc., Chem. Commun.* **1990**, 362. (c) Ogawa, K.; Terada, T.; Muranaka, Y.; Hamakawa, T.; Ohta, S.; Okamoto, M.; Fujii, S. *Chem. Pharm. Bull. Tokyo* **1987**, *35*, 3276. (d) Hua, D. H.; Peacock, N. J.; Meyera, C. Y. *J. Org. Chem.* **1980**, *45*, 1717. (e) Charlton, J. L.; Lai, H. K.; Lypka, G. N. *Can. J. Chem.* **1980**, *58*, 458.

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In summary, we have described a practical procedure for the free-catalyzed acid derivative insertion with ethyl diazo acetate and methyl diazo phenylacetate. Due to the high stability of diazoester compounds in fluorinated alcohols (HFIP and TFE), the reaction is possible under mild conditions to afford a wide range of α-acetoesters and depsipeptides. Furthermore the insertion reaction with noncarboxylic acids such as sulfonic, phosphonic, and boronic acids led to new interesting sulfonate, phosphate, and boronate derivatives. The process was completely chemoselective and required no specific treatment.

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Supporting Information Available. Procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.