Barbier Conditions for Reformatsky and Alkylation Reactions on Trifluoromethyl Aldimines

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Abstract: β-Trifluoromethyl β-amino acids and α-trifluoromethyl α-alkyl amines can be easily prepared under Barbier conditions from trifluoromethyl aldimines in moderate to good yields. β-Trifluoromethyl β-amino acids were obtained in good enantioselectivity from the chiral trifluoromethyl aldimine starting material.

Key words: Barbier reaction, Reformatsky, fluoroalkyl amines, amino acids

β-Amino acids have received great attention due to their potential medicinal and synthetic applications.[1] Considering the expected benefits of the fluorine substitution, β-fluoroalkyl β-amino acid derivatives, when incorporated into peptide sequences, are expected to modify properties and enhance resistance toward proteolysis. In this context they recently aroused great interest and numerous groups have designed new synthetic methodologies, with the objective of obtaining pure stereomers.[2] Among them, methods involving nucleophilic additions on trifluoromethyl imines[3] or related derivatives (oxazolidines,[4a] pyruvates,[5] imidoyl chlorides,[6] etc.) appeared to be powerful approaches. Most of the methods used to access the β-CF_3 β-amino acid derivatives involve addition of ester enolates,[7] Mannich-type[4] and Reformatsky[4,8] reactions. This latter reaction, performed on trifluoromethyl aldimine derivatives,[4,8a] proceeds in moderate yield and provides, as main products, corresponding azetidinones resulting from a cyclization of the intermediate metalloamine. Considering that this is probably due to the reaction conditions (THF reflux, reagent excess), we revisited the Reformatsky reaction on trifluoromethyl aldimines under milder conditions.

We have previously reported that allylation reactions on trifluoromethyl aldimines proceeded smoothly in dimethylformamide at room temperature when performed under Barbier conditions.[9]

Similar conditions were evaluated for the Reformatsky reaction performed on the *N*-(*p*-methoxyphenyl) aldimine **1** and the *N*-benzyl aldimine **2**. The reaction was conducted in DMF at room temperature with three equivalents of ethyl bromoacetate in the presence of 1.5 equivalents of granular zinc activated by a small amount of TMSCl.[9] Reaction times were long and the conversion incomplete (ca. 65–70% conversion) (Table 1, entries 1 and 3). Large excess of ethyl bromoacetate (6 equiv) and of zinc (5 equiv) were required to obtain a complete conversion in 4–5 hours. Only one product was obtained. Corresponding β-amino esters **3** and **4** were isolated in high yields (Table 1, entries 2 and 4).

Since the addition of alkyl organometallic reagents on CF_3 imine derivatives has been less studied than that of unsaturated ones (phenyl, allyl, vinyl),[10] these easy Barbier conditions have also been applied to the addition of simple alkyl halides to aldimines **1** and **2**. We first investigated the addition of isopropyl iodide on the aldimine **1** in DMF. With 2.5 equivalents of the alkyl iodide and 1.5 equivalents of Zn, the corresponding trifluoromethyl amine **5a** (Table 1, entry 5) was obtained in an excellent yield (95%). The reaction was then generalized to other alkyl halides. Under the same conditions, the reaction was less efficient with primary alkyl halides, $C_5H_{11}I$ or EtI, which required longer reaction time, and provided poor yields of amines. As for reaction with ethyl bromoacetate, by using larger excesses of halides (6 equiv) and zinc (5 equiv), **5b** and **5c** could be obtained in 70% and 97% yields, respectively (Table 1, entries 6 and 7). It is worth noting that competitive reduction products, which are generally obtained by the addition of alkyl Grignard reagents to nonfluorinated aldimines,[11] were not detected from **2** under these conditions.[12]

When performed onto the *N*-benzyl trifluoromethyl aldimine **2**, the addition of various alkyl iodides afforded the corresponding amines **6** in moderate to low yields after 24 hours (Table 1, entries 9–11) or no reaction occurred at all even with excess of reagents (Table 1, entries 10–12).

These reactions were then investigated with the methyl ether of the (*R*)-phenylglycinol trifluoromethyl aldimine **7**, which provided excellent stereoselectivity in allylation reactions under Barbier conditions.[9]

In DMF, the product **8** resulting from the addition of isopropyl iodide (3 equiv) in the presence of zinc (2.5 equiv) was obtained in a 72% yield and a poor selectivity (de = 53%; Scheme 1). The configuration of **8** proved to be *R*,*R* (see below).

Under the conditions presented in Table 1, the Reformatsky reaction performed between ethyl bromoacetate (6 equiv) and **7** failed. Replacement of DMF by THF resulted in a complete reaction and a good diastereoselectivity (de = 80%) but a longer reaction time (>20 h) was

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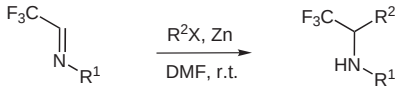
Table 1 Reformatsky and Alkylation Reactions under Barbier Conditions

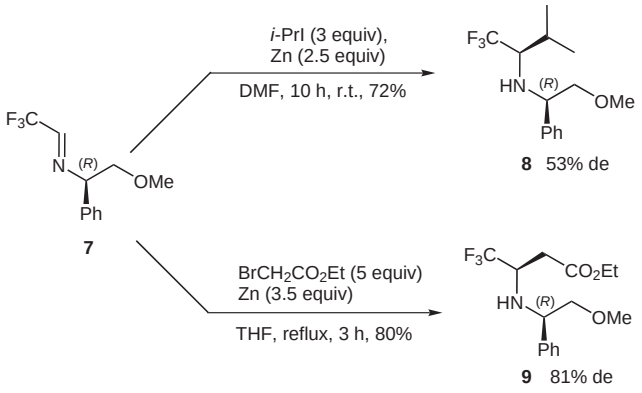


1 R^1 = PMP
2 R^1 = Bn

3–6

Entry	Imine (R^1)		R^2X (equiv)	Zn (equiv)	Time (h)	Prod.	Yield (%)
1	**1**	PMP	$EtOCOCH_2Br$ (3)	1.5	10	**3**	69[a]
2	**1**	PMP	$EtOCOCH_2Br$ (6)	5	4	**3**	80
3	**2**	Bn	$EtOCOCH_2Br$ (3)	1.5	24	**4**	66[a]
4	**2**	Bn	$EtOCOCH_2Br$ (6)	5	5	**4**	86
5	**1**	PMP	*i*-PrI (2.5)	1.5	2	**5a**	95
6	**1**	PMP	$C_5H_{11}I$ (6)	5	7	**5b**	70
7	**1**	PMP	EtI (6)	5	10	**5c**	97
8	**1**	PMP	*t*-BuI (2.5)	1.5	3	**5d**	72
9	**2**	Bn	*i*-PrI (3)	2.5	24	**6a**	59
10	**2**	Bn	$C_5H_{11}I$ (6)	5	24	**6b**	trace
11	**2**	Bn	EtI (6)	5	24	**6c**	33
12	**2**	Bn	*t*-BuI (6)	5	24	**6d**	trace

[a] The starting material was also obtained.



Scheme 1

required. Surprisingly an increased reaction rate (3 h) was obtained in refluxing THF without changing the course of the reaction. The only products formed were β-amino esters **9** obtained in 80% yield and with a good diastereoselectivity (de = 81%, determined by ^{19}F NMR of the crude; Scheme 1). Each diastereomer could be easily separated by flash chromatography to afford 69% isolated yield of the major isomer and 10% isolated yield of the minor one.[13] These results suggest that neither high temperature nor excess of Zn are responsible of the conversion of β-amino esters into azetidinones. The major isomer was obtained in the free form after deprotection of the chiral auxiliary and the hydrolysis of the ester function. This was achieved in 80% yield in a three-step procedure involving the reaction with BBr_3,[14] $Pb(OAc)_4$ and HCl (6 N) hydrolysis[4a] (Scheme 2). The *R*-configuration of the β-trifluoromethyl-β-amino acid **10** obtained was assigned by comparison of its data with the data and the optical rotation reported in the literature {$[\alpha]_D^{21}$ +25 (*c* = 0.5, 6 N HCl), $[\alpha]_D^{25}$ +26.6 (*c* = 0.5, 6 N HCl)[4a]}.

Scheme 2

In conclusion, we have described an easy method to introduce an alkyl group directly on trifluoromethylated aldimines under Barbier conditions and to perform an efficient Reformatsky reaction with an improved chemoselectivity and a good stereoselectivity. This provided a concise access to enantiopure β-trifluoromethyl β-amino acids.

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(12) Addition of EtMgBr (1.3 equiv, 1 N THF) to CF_3 aldimine **2** led to a mixture of products [$CF_3CH(Et)NHBn$: 42%; CF_3CH_2NHBn: 13%; **2**: 33%, side products: 13%].
(13) **Typical Procedure for the Synthesis of 4,4,4-Trifluoro-3-(2-methoxy-1-phenylethylamino)butyric Acid Ethyl Ester (9)**: The methyl ether of the (*R*)-phenylglycinol trifluoromethyl aldimine **7** (1 mmol, 231 mg) was dissolved in THF (5 mL) and kept under argon. Ethyl bromoacetate (6 equiv, 6 mmol, 1 g) and granular zinc (5 equiv, 5 mmol, 327 mg) were then introduced, followed by a few drops of TMSCl. After being stirred at reflux for 3 h, the reaction mixture was quenched with a sat. NH_4Cl solution (15 mL) and extracted with Et_2O (3 × 5 mL). The organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (cyclohexane–Et_2O, 80:20) to afford a mixture of two diastereomers of **9** (80%, 255 mg).
Major Diastereomer: yellow oil; yield: 69%; $[\alpha]_D^{22}$ –25.0 (*c* = 0.20, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H), 2.10 (br s, 1 H), 2.56 (dd, *J* = 6.5, 15.7 Hz, 1 H), 2.72 (dd, *J* = 4.3, 15.8 Hz, 1 H), 3.38 (s, 3 H), 3.40 (dd, *J* = 5.3, 7.9 Hz, 1 H), 3.52 (m, 1 H), 4.11 (dd, *J* = 5.5, 7.8 Hz, 2 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 7.36 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.6, 54.2 (q, J_{CF} = 29 Hz, *C*HCF_3), 58.7, 60.0, 61.0, 77.8, 125.8 (q, J_{CF} = 281 Hz, CF_3), 127.8, 128.0, 128.5, 139.4, 170.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –76.30 (d, *J* = 7.6 Hz, CF_3). IR: 2984, 1735 cm^{-1}.
Minor Diastereomer: yellow oil; yield: 10%; $[\alpha]_D^{22}$ +12.5 (*c* = 0.16, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.0 Hz, 3 H), 2.87 (dd, *J* = 2.6, 15.0 Hz, 1 H), 3.05 (dd, *J* = 5.6, 14.9 Hz, 1 H), 3.31 (s, 3 H), 3.53 (dd, *J* = 4.9, 9.8 Hz, 1 H), 3.85 (m, 1 H), 4.03 (t, *J* = 9.9 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 4.53 (dd, *J* = 5.3, 9.9 Hz, 1 H), 7.27 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 49.5, 51.5 (q, J_{CF} =35 Hz, $CHCF_3$), 58.7, 60.0, 61.4, 72.2, 124.1 (q, J_{CF} = 278.8 Hz, CF_3), 127.7, 128.0, 128.6, 135.8, 165.5. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –76.0 (d, *J* = 5.9 Hz, CF_3). IR: 2932, 1768 cm^{-1}.
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