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Synthesis of β-amino esters using the Reformatsky reaction with α-amino nitriles

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Summary — The chemical behavior of α-amino nitriles towards the Reformatsky reagent has been studied. Under certain conditions, secondary aliphatic α-amino nitrile derivatives yielded a mixture of four products consisting of a β-amino ester, a β-lactam, a bulky tertiary amine and a cinnamic derivative. In an aliphatic and an alicyclic, fully nitrogen-substituted example, a β-aminoester is obtained in high yield as the sole product.

α-amino nitrile / β-amino ester / Reformatsky reaction

Résumé — Synthèse de β-aminoesters à partir de la réaction de Réformatsky sur les α-aminonitriles. Le comportement chimique des α-aminonitriles soumis aux conditions de la réaction Réformatsky a été étudié. Dans ces conditions, les α-aminonitriles tertiaires alicycliques ou aliphatiques conduisent aux β-aminoesters correspondants avec de bons rendements. Les α-aminonitriles secondaires conduisent à un mélange de β-aminoesters, de β-lactame, une amine tertiaire et un dérivé de l'acide cinnamique.

α-aminonitrile / β-aminoester / reaction Réformatsky

Introduction

In its classical form, the Reformatsky reaction involves the zinc-induced formation of β-hydroxyalkanoates from ethyl haloacetates and aldehydes or ketones [1]. α-Amino nitriles are extremely versatile synthons, easily obtained from the Strecker synthesis and frequently used in the synthesis of amino acids. We have recently exploited the virtues of such intermediates to construct substituted isoquinolinol derivatives, which upon further reaction led to the benzo[c]phenanthridine ring system [2a,b]. To the best of our knowledge, the Reformatsky-type reaction between α-bromo esters and α-amino nitriles has received no attention. Looking for organic intermediates containing more convenient functional groups for a straightforward access to our substituted structures, we herein describe the results of our studies using α-amino nitriles as carbanionic acceptor.

Results and discussion

We first considered the reaction with one of our intermediates **1a** under previously described reaction conditions [2]. The metal is activated using trimethylchlorosilane (TMCS) [3] and the reaction is conducted in the presence of ethyl bromoacetate in dimethoxymethane (DMM) at room temperature. The first attempts led to the isolation of mixtures of three products (scheme 1 and table I). Two main products were isolated: a β-amino ester **2a**, apparently resulting from a nucleophilic displacement of the cyano group of **1** and the β-lactam **3** resulting from an intramolecular nucleophilic attack. The third product, obtained in a low yield, was identified as the cinnamic ester derivative **4**.

The cyano group is known to react with the Reformatsky reagent to yield the corresponding β-keto ester [4]. In our reaction, which gave **2a**, no nucleophilic addition occurred on the cyano function. The formation of the β-aminoester **2a** is explained either by the direct nucleophilic displacement of the nitrile group borne on the α-carbon or the indirect nucleophilic addition on a transient imine. It has been reported that nitriles, in which the cyano group is weakly bonded to α-carbons, react with carbanionic species, such as the Grignard reagent, in a coupling process [4]. An intermediate nucleophilic imine addition has been proposed for the case of Grignard addition [4]. In a second step, an intramolecular nucleophilic reaction led to **3**. The two steps were only observed when the combination of trimethylchlorosilane (as zinc-activating reagent) and dimethoxymethane as solvent were used.

Similar results have previously been recorded using a nucleophilic Reformatsky-type attack on an

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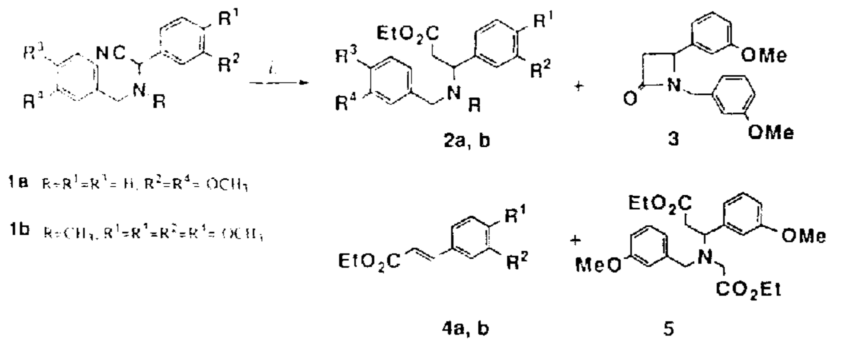


Scheme 1. *i* Zn, $BrCH_2CO_2Et$, TMCS, DMM.

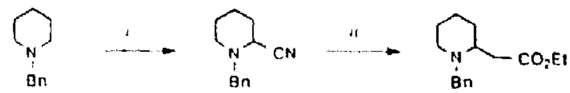
Table I. Reaction of *α*-aminonitriles **1a**, **1b** and **6** with the Reformatsky reagent (Zn, $BrCH_2CO_2Et$).

Substrate	*Solvent-metal activation*	*Zn-TMCS-$BrCH_2CO_2Et$* ratio	*Yields (%)*[a] 2a,b/7	3	4	5
1a	DMM, TMCS	3.3:0.33:3.3	16	33	12	
1a	DMM, TMCS	6.6:0.66:6.6	30	53	5	6
1a	Dioxane US-TMCS	6.6:0.66:6.6	16	15	3	
1a	Dioxane TMCS	6.6:0.66:6.6	17	5	3	35
1b	DMM, TMCS	3.3:0.33:3.3	87			
6	DMM, TMCS	3.3:0.33:3.3	89			

[a] Yields of isolated products isolated after chromatographic separation.

amine in the presence or not of a catalytic amount of trimethylchlorosilane in benzene or dimethoxymethane as solvents [5a,b]. In a recent work, additions of Reformatsky reagents to imines in the presence of 1-trimethylsilylbenzotriazole afforded β-amino esters [5c]. Other authors have used amino trimethylsilyl derivatives as intermediates for the preparation of the monobactam antibiotic, thienamycin [6]. In our case, a possible transient silylated intermediate could enhance the reactivity of our secondary amine leading to the β-lactam structure. Attempts to improve this cyclisation led us first to use increasing amounts of organozinc and activator reagents (table I). Besides the three compounds previously isolated an unexpected tertiary amine **5** was identified. Substituting the solvent, still in the presence of TMS, with a polar or less polar solvent such as tetrahydrofuran or benzene, was unfruitful. A striking improvement was observed when dioxane was used. Dioxane is known to be a poor solvent for the Reformatsky reaction except when ultrasonic (US) activation is associated [7]. Under these conditions our reaction failed. When TMCS was added, in conjunction with ultrasonic activation, the reaction led to an increase in the yield of **2a**. Without ultrasonic activation the main product isolated turned out to be the tertiary amine **5**. The presence of **4** may be explained through a retro-Michael reaction, with the loss of 3,4-dimethoxybenzylamine.

In order to extend the scope of this reaction, tertiary amines were studied as substrates. Under the usual conditions described above (table I), **1b** yielded a sole product **2b**. Surprisingly, after purification of **2b** by column chromatography (silica gel, cyclohexane-ethyl acetate, 98:2 as eluent), a second product **4b**, corresponding to an elimination product, was isolated in very low yield, while with the identical reaction performed on the alicyclic compound **6** [8], only one product **7** was obtained in very high yield (scheme 2).



6 7

Scheme 2. *i* $(PhO)_2$, Me_3SiCN; *ii* Zn, $BrCH_2CO_2Et$, TMCS, DMM.

Conclusions

In conclusion, the Reformatsky reaction with a secondary aliphatic α-amino nitrile led to an unexpected mixture of two different amines, a β-lactam and a cinnamate derivative. Starting from tertiary amine analogues, this route represents a very facile access to functionalized amines when a β-amino ester synthon is required. Further investigations toward the application of this synthesis are currently in progress in our laboratory.

Experimental section

The ^1H and ^{13}C NMR spectra were recorded in deuterochloroform solutions (except when stated otherwise) on a JEOL GSX 270 WB spectrometer at 270.5 and 68 MHz respectively. Chemical shifts are reported in ppm relative to tetramethylsilane in deuterochloroform, except where otherwise specified. IR spectra were recorded on Perkin-Elmer 580 or 457 spectrophotometers using potassium bromide discs for solids, or neat liquid films for liquids. Only significant IR bands are quoted. Melting points were determined on a Electrothermal 8100 melting point apparatus and are uncorrected. HR mass spectra were determined on a high-resolution Varian MAT 311 or MS/MS ZabSpec TOF Micromass at 70 eV or using FAB.

General procedure

To a suspension of zinc dust (15.8 g) in dimethoxymethane (60 mL) under nitrogen, trimethylchlorosilane was added (2.80 mL, 0.024 mol) and the resulting mixture was stirred at room temperature for 15 min and then under reflux for 5 min. The suspension was cooled, and a solution of ethyl bromoacetate (27 mL, 0.24 mol) in dimethoxymethane (30 mL) is slowly added at such a rate that the solvent gently refluxes. After being heated to reflux for 2 h, the dark green solution is cooled and the corresponding amino nitrile **1** (0.073 mol) added. The mixture is then stirred for 6 h at room temperature. The mixture is poured over a solution of NH_4Cl (40 mL, saturated solution) and the organic layer is separated, eliminated under reduced pressure, and 30 mL of dichloromethane is added. The organic layer is washed three times with water (20 mL), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give an oily residue, which is then purified by column chromatography (cyclohexane/ethyl acetate: 70:30 to 95:5 and Merck 60H silica gel, 70–230 mesh).

• *Ethyl 3-[(3-methoxybenzyl)amino]-3-(3-methoxyphenyl)propanoate* **2a**

IR (KBr): ν(C=O) 1 720 cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): 1.20 (t, CH_2 CH_3, 3H, J = 7.5 Hz); 2.25 (broad s, NH); 2.62 (dd, CH CH_2 CO_2Et, 1H, J = 15.5 Hz, J = 9.0 Hz); 2.68 (dd, CH CH_2 CO_2Et, 1H, J = 15.5 Hz, J = 5.00 Hz); 3.52 (d, Ar CH_2 N, 1H, J = 13.5 Hz); 3.68 (d, Ar CH_2 N, 1H, J = 13.5 Hz); 3.79, 3.81 (s, OCH_3, 6H); 4.1 (q, CH_2 CH_3, 2H, J = 7.5 Hz); 4.10 (dd, N CH Ar, 1H, J = 5.0 Hz, J = 9.0 Hz); 6.75–6.95 (m, *aromatic H*, 6H); 7.15–7.29 (m, *aromatic H*, 2H).

^{13}C NMR ($CDCl_3$, 68 MHz): 14.1 [OCH_2CH_3]; 42.9 [CH CH_2]; 51.1 [Ar CH_2 N]; 55.1, 55.2 [OCH_3]; 58.7 [N CH Ar]; 60.5 [O CH_2 CH_3]; 112.4, 112.5, 112.9, 113.5, 119.4, 120.3, 129.2, 129.5 [*aromatic CH*]; 141.7, 141.9, 159.6, 159.8 [*aromatic C*]; 171.7 [C=O].

MS-IE: m/z (%): 343 (M^+, faible) 342 (M − H$^+$, 4), 256 (60), 136 (62), 121 (100).

HR-MS: calc for (M − H$^+$) 342.1705, found 342.1717.

• *Ethyl 3-[(3,4-dimethoxybenzyl)methylamino]-3-(3,4-dimethoxyphenyl)propanoate* **2b**

IR (KBr): ν(C=O) 1 720 cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): 1.19 (t, CH_2 CH_3, 3H, J = 7.5 Hz); 2.12 (s, N CH_3); 2.72 (dd, CH CH_2 CO_2Et, 1H, J = 14.6 Hz, J = 7.5 Hz); 3.03 (dd, CH CH_2 CO_2Et, 1H, J = 14.6 Hz, J = 8.0 Hz); 3.24 (d, Ar CH_2 N, 1H, J = 13.0 Hz); 3.50 (d, Ar CH_2 N, 1H, J = 13.0 Hz); 3.86, 3.88, 3.89, 3.90 (s, OCH_3, 12H); 4.10 (q, CH_2 CH_3, 2H, J = 7.5 Hz); 4.16 (dd, N CH Ar, 1H, J = 7.5 Hz, J = 8.0 Hz); 6.78–6.86 (m, *aromatic H*, 6H).

^{13}C NMR ($CDCl_3$, 68 MHz): 14.1 [OCH_2CH_3]; 37.6 [N CH_3]; 37.9 [CH CH_2]; 55.7 [OCH_3], 55.8 [OCH_3]; 55.9 [2C, OCH_3]; 58.1 [Ar CH_2 N]; 60.3 [O CH_2 CH_3]; 63.9 [N CH Ar]; 110.5, 110.6, 111.7, 120.4, 120.6 [*aromatic CH*]; 130.9, 132.4, 147.9, 148.2, 148.5, 148.8 [*aromatic C*]; 171.9 [C=O].

HR-FAB (positive) MS: calc 418.223, found 418.223 (M + H$^+$).

• *1-(3-Methoxybenzyl)-4-(3-methoxyphenyl) azetidin-2-one* **3**

IR (KBr): ν(C=O) 1 750 cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): 2.72 (dd, CO CH_2 CH, 1H, J = 14.6 Hz, J = 2.2 Hz); 3.34 (dd, CO CH_2 CH, 1H, J = 14.6 Hz, J = 5.2 Hz); 3.76, 3.78 (s, OCH_3, 6H); 3.78 (d, Ar CH_2 N, 1H, J = 15 Hz); 4.39 (dd, N CH Ar, 1H, J = 5.2 Hz, J = 2.2 Hz); 4.75 (d, Ar CH_2 N, 1H, J = 15 Hz); 6.60–6.80 (m, *aromatic H*, 6H); 7.20–7.40 (m, *aromatic H*, 2H).

^{13}C NMR ($CDCl_3$, 68 MHz): 42.1 [CO CH_2 CH]; 46.7 [Ar CH_2–N]; 53.5 [N–CH–Ar]; 55.1, 55.2 [OCH_3]; 111.7, 113.3, 113.8, 113.9, 118.7, 120.7, 129.7, 130.0 [*aromatic CH*]; 136.9, 139.5, 159.7, 159.9 [*aromatic C*]; 167.0 [C=O].

MS-IE: m/z (%): 297 (M^+, 31), 134 (100), 121 (26), 91 (22).

HR-MS: calc 297.1365, found 297.1369.

• *Ethyl trans-3-(3,4-dimethoxyphenyl)prop-2-enoate* **4** *[9]*

IR (KBr): ν(C=O) 1 685 cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): 1.31 (t, CH_2 CH_3, 3H, J = 7.5 Hz); 3.83 (s, OCH_3, 6H); 4.26 (q, CH_2 CH_3, 2H, J = 7.5 Hz); 6.12 (d, CH=CH, 1H, J = 16 Hz); 6.93 (d, *H aromatic*, 1H, J = 8.5); 7.04 (d, *H aromatic*, 1H, J = 2.3 Hz); 7.42 (dd, *aromatic H*, 1H, J = 8.5 Hz, J = 2.3 Hz); 7.65 (d, CH=CH, 1H, J = 16 Hz).

^{13}C NMR ($CDCl_3$, 68 MHz): 14.3 [OCH_2 CH_3]; 55.9 [OCH_3]; 55.8 [OCH_3]; 46.7 [OCH_2 CH_3]; 109.5, 110.9, 122.5 [*aromatic CH*]; 115.9, 144.5 [*CH*=]; 127.3, 149.1, 151.0 [*aromatic C*]; 167.2 [C=O].

MS-IE: m/z (%): 236 (M^+, 65), 191 (100), 163 (27), 28 (26).

HR-MS: calc 236.1048, found 236.1048.

• *Diethyl 3-(3-methoxybenzyl)-4-(3-methoxyphenyl)-3-azahexanedioate* **5**

IR (KBr): ν(C=O) 1 720 cm^{-1} (broad).

^1H NMR ($CDCl_3$, 270 MHz): 1.15 (t, CH_2 CH_3, 3H, J = 7.3 Hz); 1.22 (t, CH_2 CH_3, 3H, J = 7.3 Hz); 2.71 (dd, CH CH_2 CO_2Et, 1H, J = 14.5 Hz, J = 8.2 Hz); 3.00 (dd, CH CH_2 CO_2Et, 1H, J = 14.5 Hz, J = 6.8 Hz); 3.16 (d, N CH_2 CO_2Et, 1H, J = 17.2 Hz); 3.38 (d, N CH_2 CO_2Et, 1H, J = 17.2 Hz); 3.59 (d, Ar CH_2 N, 1H, J = 14.0 Hz); 3.79 (d, Ar CH_2 N, 1H, J = 14.0 Hz); 3.79, 3.80 (s, OCH_3, 6H); 4.05 (q, CH_2 CH_3, 2H, J = 7.3 Hz); 4.10 (q, CH_2 CH_3, 2H, J = 7.3 Hz); 4.32 (dd, N CH Ar, 1H, J = 8.2 Hz, J = 6.8 Hz); 6.70–6.95 (m, *aromatic H*, 6H); 7.10–7.30 (m, *aromatic H*, 2H).

^{13}C NMR ($CDCl_3$, 68 MHz): 14.0 [OCH_2CH_3]; 14.2 [OCH_2CH_3]; 37.9 [CH CH_2]; 54.2 [N CH_2 CO_2Et]; 54.7 [Ar CH_2 N]; 55.1, 55.2 [OCH_3]; 60.3, 60.4 [O CH_2 CH_3]; 61.4 [N CH Ar]; 112.7, 112.9, 114.0, 114.0, 120.5, 120.9, 129.4, 129.2 [*aromatic CH*]; 140.7, 141.9, 159.5, 159.6 [*aromatic C*]; 171.3, 171.5 [C=O].

MS-IE: m/z (%): 384 (faible), 356 (44), 121 (100).

HR-FAB (positive) MS: calc 430.223, found 430.223.

- *1-Benzylpiperidine-2-carbonitrile* **6**

IR (KBr): ν(C≡N) 2215 cm^{-1}.

^{1}H NMR (CDCl$_3$, 270 MHz): 1.55–1.95 (m, CH_2, 6H); 2.43 (m, CH_2–N, 1H); 2.80 (m, CH_2–N, 1H); 3.53 (d, Ar–CH_2–N, 1H, J = 13.2 Hz); 3.69 (d, Ar–CH_2–N, 1H, J = 13.2 Hz); 3.73 (t, CH–CN, 2H, J = 3.5 Hz); 7.25–7.35 (m, *aromatic H*, 5H).

^{13}C NMR (CDCl$_3$, 68 MHz): 20.1, 21.9, 28.5, 60.7 (*alicyclic* CH_2); 49.7 (Ar–CH_2–N); 52.0 (CH–CN); 116.7 (CN); 127.5, 128.4, 128.9 (*aromatic CH*); 136.9 (*aromatic C*).

- *Ethyl 1-Benzylpiperidine-2-acetate* **7**

IR (KBr): ν(C=O) 1720 cm^{-1}.

^{1}H NMR (CDCl$_3$, 270 MHz): 1.24 (t, CH_2–CH_3, 3H, J = 7.3 Hz); 1.35–1.85 (m, CH_2, 6H); 2.18 (m, CH_2–N, 2H); 2.44 (dd, CH–CH_2–CO_2Et, 1H, J = 14.6 Hz, J = 8.0 Hz); 2.72 (dd, CH–CH_2–CO_2Et, 1H, J = 14.6 Hz, J = 5.0 Hz); 2.98 (m, CH–CH_2–CO_2Et, 1H); 3.37 (d, Ar–CH_2–N, 1H, J = 13.5 Hz); 3.82 (d, Ar–CH_2–N, 1H, J = 13.5 Hz); 4.13 (q, CH_2–CH_3, 2H, J = 7.3 Hz); 6.78–6.86 (m, *aromatic H*, 5H).

^{13}C NMR (CDCl$_3$, 68 MHz): 14.1 (OCH_2CH_3); 22.2, 25.4, 30.8, 58.4 (*alicyclic* CH_2); 36.1 (CH–CH_2); 50.6 (Ar–CH_2–N); 57.5 (CH–CH_2); 60.3 (O–CH_2–CH_3); 126.7, 128.0, 128.4, 128.6 (*aromatic CH*); 139.4 (*aromatic C*); 172.8 (C=O).

MS-EI: m/z (%): 261 (M^+, weak), 171 (100), 91 (74).

HR-MS: calc 261.1729, found 261.1715

Acknowledgments

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