Molecules **2008**, *13*, 716-728

molecules

ISSN 1420-3049

www.mdpi.org/molecules

Full Paper

An Efficient Synthesis of γ-Aminoacids and Attempts to Drive Its Enantioselectivity

Salvador Gil, Margarita Parra* and Pablo Rodríguez

Department de Organic Chemistry, Universitat de València, Dr. Moliner 50, 46100 Burjassot, Spain. Fax +34(9)63543831; E-mails: Salvador.gil@uv.es; roapa@alumni.uv.es

* Author to whom correspondence should be addressed; E-mail: Margarita.Parra@uv.es

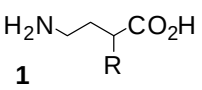
Received: 10 March 2008; in revised form: 26 March 2008 / Accepted: 26 March 2008 / Published: 27 March 2008

Abstract: Addition of carboxylic acid dianions to bromoacetonitrile lead, in good yields, to the corresponding γ-cyanoacids, which on hydrogenation yielded γ-aminoacids. This two step methodology improves upon previously described results. Poor *e.e*'s resulted from our attempts to drive the enantioselectivity of this transformation by chiral amide induction.

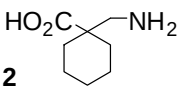
Keywords: GABA, γ-aminoacids, bromoacetonitrile, enediolate, regioselectivity.

Introduction

4-Aminobutanoic acid (GABA, **1**, R=H) is the main inhibitory neurotransmitter in the mammalian central nervous system and in the retina [1]. GABA acts at inhibitory synapses in the brain and by binding to specific transmembrane receptors in the plasma membrane of both pre- and postsynaptic neurons. This binding causes the opening of ion channels to allow either the flow of negative ions into the cell or positively-charged ions out of the cell. There is growing evidence that GABA participates in another slower and more diffuse form of signaling often referred to as ionic inhibition [2].



1



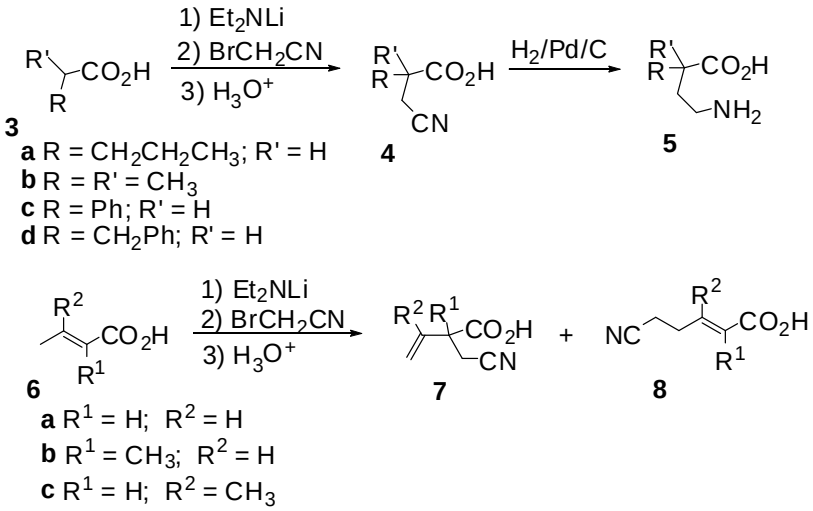
2

On the other hand, the racemic 2-methyl (**1**, R=CH_3) and 2-phenyl (**1**, R=Ph) derivatives were shown to inhibit binding of the clinically effective anticonvulsant gabapentin **2** to synaptic plasma membranes of the rat cerebral cortex [3]. These facts have prompted a high demand for the synthesis of γ-amino acids [4] and, in particular of analogs bearing a phenyl group (**1**, R=Ph) in the α, β, or γ-positions [5].

Some authors have developed stereoselective syntheses of these compounds from a chiral ester using a deracemization strategy. The ester is obtained from a racemic acid via protection, alkylation of the corresponding enolate and hydrolysis (reported combined yields 60-70%), followed by esterification with a chiral auxiliary, deracemization and a new hydrolysis under essentially non-racemizing conditions. One of the chiral auxiliaries giving best results is (*R*)-pantolactone [6].

Our experience in the direct alkylation of enediolates of carboxylic acids [7], led us to consider the feasibility of a direct synthesis of racemic γ-aminoacids by reaction with bromoacetonitrile. Upon catalytic hydrogenation, the obtained γ-cyanoacids allow a rapid and easy access to γ-aminoacids, thus avoiding the commonly used protection-deprotection sequences (Scheme 1) [8].

Scheme 1: Reaction of bromoacetonitrile with saturated and unsaturated carboxylic acids.



On the other hand, our studies on enantioselectivity induction of this alkylation, by using chiral amides both as bases and chiral auxiliaries [9], led us to think that chiral γ-aminoacids might be obtained in two steps. We report here this approach to the synthesis of γ-aminoacids.

Results and Discussion

Carboxylic acids are synthetically useful building blocks because, after double deprotonation, they afford enendiolates (or dienediolates when starting from α,β-unsaturated carboxylic acids) that can react with various electrophiles under appropriate conditions [10]. Lithium dialkylamides are commonly used as bases to generate the lithium dianions [10,11], due to their strength and low nucleophilicity, specially when derived from sterically hindered amines, combined with their solubility in non-polar solvents [11,12]. It is well established that, in these solvents, lithium enolates exist as

complex ion pair aggregates, whose metal center may be coordinated to solvent molecules or other chelating ligands, such as the amines resulting from deprotonation of the acid by the lithium amide. The available data confirm the complexity present in those aggregated reactive species, whose reactivity and selectivity products can be influenced by many factors [9-13]. Thus, an optimization study for each new electrophile is typically required.

We began describing the optimization of the alkylation reaction of enediolates and dienediolates of carboxylic acids with bromoacetonitrile (Scheme 1). From our experience on the addition of carboxylic acids to alkyl halides [7] and nitriles [14], we knew that the first is a fast reaction, which may be completed at low temperature, whereas the latter is a reversible process that requires a final exoergonic step for the reaction to progress. Here, having both a nitrile and a halide in the same electrophile, an optimization of reaction was required in order to drive the reaction towards the alkylated product. We have focused the optimization study in three variables: reaction time, type of amine used to generate the lithium amide and the amount of this amine. Valeric, isobutyric, phenylacetic and hydrocinnamic acids **3a-3d** were used in this study.

On the other hand, we have extended this methodology to α,β-unsaturated carboxylic acids, whose double deprotonation lead to dienediolates that behave as ambident nucleophiles through their α or γ carbon atoms [10]. Although α attack predominates for irreversible reactions, strong deviations are observed in alkylation reactions [7], that should be avoided in this case because only α–products would lead to the corresponding γ-aminoacid. From the results shown in Table 1 we have found that the optimized standard conditions are 24 h at room temperature using 10 mol % of diethylamine. Use of other amines was not advantageous.

Previous studies lead us to develop sub-stoichiometric amide conditions for the generation of dianions of carboxylic acids which, in some cases improve the yield and selectivity of the reaction. We have optimized a complete generation of dianions of carboxylic acids by using an equimolecular amount of *n*-BuLi combined with a sub-stoichiometric amount of amine. A small amount of amine is necessary to promote the deprotonation without nucleophilic addition of the n-BuLi to the carboxylic group (the lower limit is around 10%). A catalytic cycle is possible because a carboxylate and the corresponding dianion can be held together without self-condensation [15], this is an advantage of enediolates over simple enolates, especially those derived from esters. These conditions are especially adequate when the electrophile is attacked quicker by the lithium amide than by the dianion.

Among the various amines tested, namely disopropylamine (entry 2), cyclohexylisopropylamine (entries 5 and 9), 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (entry 3), diethylamine proved to be the most efficient for this reaction. As shown in Table 1, in some cases yields are better when an equimolecular amount of amine is used. Although no explanation has been found, it is well known that some dianions of carboxylic acids undergo an easy deprotonation by the amide while others do not. We think that this factor is crucial to determine whether yields are higher with sub-stoichiometric or with equimolecular amounts of amine. However, it is not easy to predict the behaviour of a particular acid due to the aggregation nature of these complex systems. In this case, good yields with equimolecular amounts of amine will be convenient for the chiral induction in the enantioselective studies described below.

Table 1. Addition of dianions of carboxylic acids to bromoacetonitrile.

Entry	Acid	Amine	Eq. Amine	Time (h)	Yield (%)	Regioselectivity α (%)	Regioselectivity γ (%)
1	**3a**	Et_2NH	2	24	0		
2	**3a**	i-Pr_2NH	2	24	0		
3	**3a**	AZA*	2	24	0		
4	**3a**	Et_2NH	0.5	24	71		
5	**3a**	i-PrCyNH*	0.5	24	70		
6	**3b**	Et_2NH	0.5	24	42		
7	**3c**	Et_2NH	2	24	85		
8	**3c**	Et_2NH	0.5	24	97		
9	**3c**	i-PrCyNH*	0.5	24	98		
10	**3d**	Et_2NH	0.5	24	78		
11	**6a**	Et_2NH	0.5	24	72	51**	49
12	**6b**	Et_2NH	2	24	77	40	60
13	**6b**	Et_2NH	0.5	24	84	60	40
14	**6c**	Et_2NH	2	12	43	100	0
15	**6c**	Et_2NH	2	17	67	100	0
16	**6c**	Et_2NH	2	24	69	100	0
17	**6c**	Et_2NH	2	48	39	100	0
18	**6c**	Et_2NH	0.5	24	80	100	0

* AZA: 1,3,3-trimethyl-6-azabiclyclo[3.2.1]octane; i-PrCyNH: cyclohexylisopropylamine.

** Double bond in product **7a** is in the 2,3-position

All products described in Table 1 were isolated in high purity after a simple work-up consisting in the separation of neutral and acidic fractions. Sometimes, small amounts of starting acid are found in the acidic fraction.

Products **4** are efficiently reduced to γ-aminoacids **5** in quantitative yield by catalytic hydrogenation and their spectroscopic data agreed with those described in the literature [6, 16]. Higher pressure and longer reaction timer were required for **4a**.

This methodology improves the results described to date that require at least two additional steps: protection and deprotection of the carboxyl group.

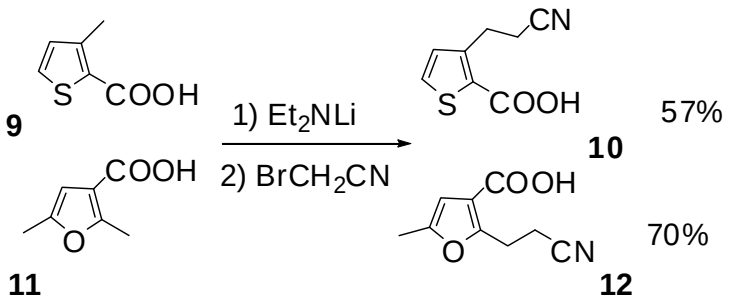
α,β-Unsaturated carboxylic acids (entries 11-18, Table 1) behave in a similar way as that observed in other alkylation reactions [7]. Only α-adducts (products **7**) are observed in the addition of dimethylacrylic acid (**6c**). Although the dianion of dimethylacrylic acid typically gives good α-regioselectivity due to stereoelectronic effects [7]; in this case this is quantitative, probably due to the fact that alkylation with bromoacetonitrile is slower. Despite this, regioselectivity cannot be controlled for the rest of acids **6** and mixtures of α and γ adducts result. The fluctuation in regioselectivity can be attributed to the presence of LiBr in the aggregates states of the dianion system; that is generated as the reaction progress [9, 17]. Koga and we have observed the influence of the LiBr in the stereoselectivity whose change to the reaction evolution. This phenomenon is explained by the parallel presence of LiBr whose concentration is low at the early stage of the reaction, but increases as the reaction

progress. It seems that the effect of the LiBr slowly released *in situ* cannot be reproduced by its external addition [17].

We would like to emphasize that the α–adduct from crotonic acid (**6a**) undergoes migration of the double bond. Such an isomerization to the thermodynamically more stable products has already been observed in allyl alkylation products [18], but a thermal activation (to at least 170ºC) was required as, under kinetic conditions, dianions reprotonate in the α–position, leading to the deconjugation of the double bond [10]. An isomerization at room temperature under basic conditions has been observed only in gamma-adducts from the addition to perfluoroketene dithioacetals [2c]. Here, the introduction of nitrile may lead to an increment of acidic positions, this is specially so for crotonic acid, and this could produce different equilibria allowing the most stable product, the conjugated one, to accumulate.

The method can be extended to *o*-methyl aromatic acids as can be seen in Scheme 2. Acids **10** and **12** are obtained in 57 and 70 % yield respectively. Unfortunately reaction with *o*-toluic and 2-methylnicotinic acids under different conditions led mainly to starting acid.

Scheme 2: Reaction of bromoacetonitrile with *o*-methyl aromatic acids.

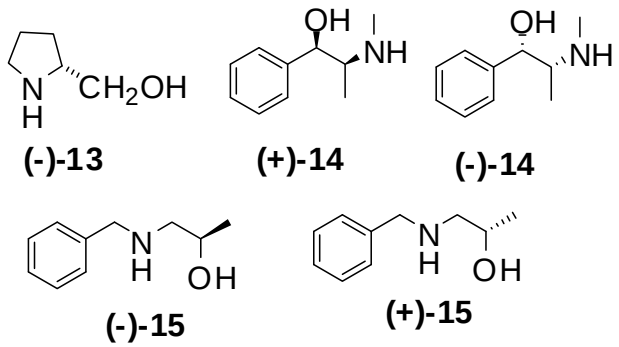


We have reported some promising results on the effect of several lithium amide bases on the stereoselectivity of the alkylation of dienediolates of unsaturated carboxylic acids [9]. Application of these bases as chiral inductors in an enantioselective synthesis of γ-aminoacids could be an important extension of the methodology described above.

The use of chiral bases as both strong bases and chiral auxiliaries has attracted considerable attention in asymmetric synthesis through enolates [19]. For example; Koga *et al.* [20] studied the alkylation of phenylacetic acid with some halides, under several conditions, using a diamine as chiral auxiliary attaining from 1 to 68% *e.e*. We have described similar results for π-extended enolates of unsaturated carboxylic acids using both enantiomers of *N*-benzyl-2-hydroxypropanamide [9]. Main advantages of this method are: simple setup and work-up of the reactions, chiral compounds can be obtained in a single step and chiral bases are easily recovered during work-up in a re-usable form.

To undertake the studies of the enantioselectivity of this reaction we have chosen the alkylation of phenylacetic acid (**3c**) with bromoacetonitrile because both cyanoacids **5c** are described in the literature [6b]. The chiral bases that have been used are depicted in Figure 2; namely, (*R*)-(-)-pyrrolidine methanol (**13**), (+) and (-)-ephedrine (**14**) and (*R*)-(-) and (*S*)-(+)-1-(benzylamino)propan-2-ol (**15**), previously synthetized by us [9].

Figure 2.



It was necessary to re-optimize the reaction conditions because an equimolecular amount of amine was required. Results are shown in Table 2. Enantiomeric excesses were determined by HPLC using a semipreparative CHIRAL PACK AD-H column.

Table 2. Addition of phenylacetic acid dianion to bromoacetonitrile using chiral lithium amides as bases.

Entry	Amine	Aditive	time/temp. h / ºC	Yield (%)	*e.e.* (%)	Major enantiomer
1	**(-)-13**		24 / 0	0		
2	Et_2NH	**(-)-13**	24 / 0	0		
3	**(+)-14**		24 / -20	95	8	(*R*)-**5c**
4	**(+)-14**		24 / -78	88	8	(*R*)-**5c**
5	**(+)-14**		3 / -78	85*	10	(*R*)-**5c**
6	**(-)-14**		3 / -78	73*	0	(*S*)-**5c**
7	**(-)-15**		24 / -20	84	8	(*S*)-**5c**
8	**(-)-15**		24 / -78	71*	6	(*S*)-**5c**
9	**(+)-15**		24 / -78	76	0	(*R*)-**5c**
10	**(+)-14**	LiCl	3 / -78	76*	6	(*R*)-**5c**
11	**(+)-14**	LiBr	3 / -78	78*	7	(*R*)-**5c**
12	**(+)-14**	LiF	3 / -78	75*	6	(*R*)-**5c**

* Around 20% of starting acid is recovered.

No reaction was observed with (-)-**13** as base and additive when following the standard conditions described above for dianion generation. A similar behaviour occurred with both enantiomers of **14** and **15**. After studying the time and temperature dependence of the enantioselectivity we concluded that similar results are observed at different temperatures but shorter reaction time improve the recovered starting acid. In all cases, the chiral induction was very poor. Some authors [20] explain that the presence of LiBr, whose concentration is low at the early stages of the reaction but increases as the reaction progresses is determinant in the stereoselectivity of reaction of enolates. Accordingly we tried to mimic this effect by addition as an external additive of two equivalents of lithium halides, but no effect was observed (entries 10-12). It seems that the effect of LiBr, slowly released *in situ* cannot be reproduced by external addition. Although similar behaviour are expected for LiCl or LiF this is not

always the case as it is known that sometimes LiCl and LiBr lead to different results and no explanation have been found [21]. Both enantiomers of the amines **14** and **15** give the antipodal enantiomer of **5**, as expected.

Conclusions

In summary, a general procedure for the addition of dianions of carboxylic acids to bromoacetonitrile is described. This methodology, with saturated carboxylic acids, is a new approach to the synthesis of γ-aminoacids that are obtained with higher yields than those described. Unfortunately, too poor *e.e*'s resulted in our attempts to drive the enantioselectivity by chiral amide induction. Despite this fact, application of deracemization process to these susbtrates would be a better choice than that described up to now in the literature.

Experimental

General

Melting points were determined with a Cambridge Instruments Hot Plate Microscope and are uncorrected. IR spectral data were obtained for liquid film or KBr discs, the measurements were carried out by the SCSIE (Servei Central de Suport a la Investigació Experimental de la Universitat de Valencia) on a Matteson Satellite FTIR 3000 model Spectrophotometer. NMR spectra were recorded at 25ºC for solutions in the stated solvent on Bruker Avance 300, 400 or 500 spectrometers. High resolution mass spectra were determined with a Fison VG Autospec spectrometer. Flash Column Silica Gel (230-400 mesh, Scharlau) was used for flash column chromatography, with hexane/ethyl acetate mixtures for elution. All reactions were carried out under argon atmospheres, in oven dried glassware, using standard conditions for exclusion of moisture. THF was freshly distilled from blue benzophenone ketyl and amines were distilled from CaH_2 and stored over molecular sieves and kept under Ar. The BuLi used was a 1.6 M hexane solution. This solution's concentration was periodically checked before use. The -78 ^oC reaction temperature was achieved by cooling with a CO_2/acetone bath and 0 ^oC achieved by an ice/water bath. Organic extracts were dried over anhydrous $MgSO_4$, and solutions were evaporated under reduced pressure with a rotatory evaporator and a bath set at 40 ^oC.

General procedure for the synthesis of β-cyanoacids

n-BuLi (1.6 M in hexane) was introduced into a previously purged reaction flask. The hexane was evaporated under vacuum and THF (2 mL), followed by diethylamine (5 or 1.25 mmol) were added at -78 ºC. The mixture was stirred for 15 min at 0 ºC. The acid (2.25 mmol) in THF (2 mL) was added slowly at -78 ºC. After 30 min at 0 ºC, bromoacetonitrile (0.16 mL, 2.25 mmol) in THF (2 mL) was added slowly at -78 ºC. The solution was stirred at room temperature for 24 h and quenched with H_2O (15 mL). The reaction mixture was extracted with Et_2O (3 x 15 mL). The aqueous phase was acidified to pH 1 with conc. HCl and then extracted with EtOAc (3 x 15 mL) and the combined extracts were

dried over anh. $MgSO_4$. After evaporation of the solvent, the cyanoacids obtained were pure enough for the following hydrogenation step.

2-(Cyanomethyl)pentanoic acid (**4a**). From valeric acid (**3a**, 230 mg); yield: 247 mg (71%); amber solid (m.p. 138-140 ºC); IR (KBr): υ= 3500-2400, 2386, 1712, 1666, 1591, 1410, 1243, 1106, 845, 765 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3CN): δ = 0.92 (t, J = 7.4 Hz, 3H, CH_3-), 1.33 (m, 2H, $CH_3C\underline{H}_2$), 1.67 (m, 2H, -$CHC\underline{H}_2$-), 1.94 (m, 1H, -$C\underline{H}CH_2$-), 2.59 (m, 1H, $C\underline{H}HCN$), 2.94 (m, 1H, $CH\underline{H}CN$) ppm; ^{13}C-NMR (75 MHz, CD_3CN): δ = 14.1 (CH_3-), 20.1 (CH_3CH_2-), 20.9 (-$\underline{C}H_2CN$), 33.4 (-$\underline{C}H_2CH_2COOH$), 41.4 (CH), 118.0 (CN), 178.7 (COOH) ppm; MS: m/z (%) = 141 (M^+, 2), 118 ($C_7H_4NO^+$, 26), 114 (M^+-HCN, 27.6), 100 ($C_7H_7N^+$, 100), 73 ($C_3H_5O_2^+$, 77), 59 ($C_2H_5NO^+$, 93); HRMS: m/z calcd. for $C_7H_{11}NO_2$ [M^+]: 141.0789; found: 141.0769.

3-Cyano-2,2-dimethylpropanoic acid (**4b**). From 2-methylpropanoic acid (**3b**, 198 mg); yield: 120 mg (42%); oil; IR (KBr): υ= 3500-2400, 2385, 1710, 1650, 1410, 1375, 1106, 845, 765 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3CN): δ = 1.32 (s, 6H, $2CH_3$), 2.64 (s, 2H, CH_2).

3-Cyano-2-phenylpropanoic acid (**4c**). From phenylacetic acid (**3c**, 306 mg); yield: 379 mg (97%); oil [6]; IR (KBr): υ= 3600-2700, 2257, 1713, 1602, 1497, 1415, 1231, 1176, 839, 724 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3CN): δ = 2.89 (dd, J_1 = 17.0 Hz, J_2 = 8.1 Hz, 1H, -$C\underline{H}HCN$), 3.01 (dd, J_1 = 17.0 Hz, J_2 = 6.9 Hz, 1H, -$CH\underline{H}CN$), 4.00 (m, 1H, $PhC\underline{H}$-), 7.3 (m, 5H, CH_{Ar}) ppm; ^{13}C-NMR (100 MHz, CD_3CN): δ = 21.0 ($\underline{C}H_2CN$), 47.4 ($Ph\underline{C}H$), 118.2 (CN), 128.1 (CH_{Ar}), 130.2 (CH_{Ar}), 133.4 (CH_{Ar}), 138.6 (C_{Ar}), 175.0 (COOH) ppm; MS: m/z (%) = 175 (M^+, 12), 136 (M^+-C_2NH, 46), 130 (M^+-COOH, 16), 104 (M^+-COOH-CN, 30), 103 (M^+-COOH-CN-H, 30), 92 ($C_7H_8^+$, 22), 91 ($C_7H_7^+$, 100), 77 ($C_6H_5^+$, 100); HRMS: m/z calcd. for $C_{10}H_9NO_2$ [M^+]: 175.0633; found: 175.0630.

2-Benzyl-3-cyanopropanoic acid (**4d**). From hydrocinnamic acid (**3d**, 338 mg); yield: 324 mg (78%); amber solid (m.p. 99-101ºC); IR (KBr): υ= 3500-2500, 3050, 2920, 2351, 1796, 1730, 1550, 1410, 1220, 693 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3CN): δ = 2.53 (dd, J_1 = 2.6 Hz, J_2 = 3.2 Hz, 2H, CH_2CN), 2.90 (m, 1H, $PhC\underline{H}H$-), 3.05 (m, 2H, $PhCH\underline{H}$-, $C\underline{H}COOH$), 7.20-7.25 (m, 5H, CH_{Ar}) ppm; ^{13}C-NMR (75 MHz, CD_3CN): δ = 19.3 ($\underline{C}H_2CN$), 37.4 ($Ph\underline{C}H_2$), 43.5 ($\underline{C}HCOOH$), 119.2 (CN), 127.9 (CH_{Ar}), 129.6 (CH_{Ar}), 130.0 (CH_{Ar}), 138.6 (C_{Ar}), 174.2 (COOH) ppm; MS: m/z (%) = 190 (M^++H, 4), 189 (M^+, 4), 149 (M^+-CH_2CN, 64.7), 131 (M^+-CH_2CN-H_2O, 64.8), 91 ($C_7H_7^+$, 100); HRMS: m/z calcd. for $C_{10}H_9NO_2$ [M^+]: 189.079; found: 189.0754.

*Reaction with crotonic acid (**6a**).* Yield: 206 mg (73 %) as a mixture of **7a** and **8a** (51:49).

2-(Cyanomethyl)but-2-enoic acid (**7a**): yellow solid (m.p. 131-133 ºC); IR (KBr): υ= 3400-2700, 2928, 2253, 1775, 1682, 1409, 1293, 1220, 1149, 927 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.00 (d, J = 7.2 Hz, 3H, CH_3), 3.40 (s, 2H, CH_2CN), 7.32 (q, J = 7.2 Hz, CH=) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.9 (CH_2), 15.6 (CH_3), 117.1 (CN), 123.0 (CH=$\underline{C}$). 146.3 ($\underline{C}$H=C), 171.0 (COOH) ppm; MS: *m/z* (%) = 125 (M^+, 7), 107 (M^+-H_2O, 3), 99 (M^+-HCN, 19), 85 ($C_4H_5O_2^+$, 42), 55 ($C_4H_7^+$, 49); HRMS: *m/z* calcd for $C_7H_9NO_2$ [M^+]: 125.0477; found: 125.0459.

5-Cyanopent-2-enoic acid (**8a**): powder (m.p. 46-51 ºC); IR (KBr): υ= 3500-2400, 2252, 1705, 1651, 1530, 1394, 1287, 1212, 969, 667 cm^{-1}; ^{1}H-NMR (300 MHz, MeOD): δ = 3.19-3.31 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2$CN), 6.60 (d, *J* = 12.0 Hz, C<u>H</u>COOH), 7.64 (dt, J_1 = 12.1 Hz, J_2 = 7.2 Hz, 1H, C<u>H</u>=CHCOOH) ppm; ^{13}C-NMR (75 MHz, MeOD): δ = 16.8 (<u>C</u>H$_2$CN), 29.1 (<u>C</u>H$_2$CH$_2$CN), 120.6 (CN), 125.3 (<u>C</u>HCOOH), 146.5 (<u>C</u>H=CHCOOH), 169.7 (COOH) ppm; MS: *m/z* (%) = 126 (M^+-H, 5), 125 (M^+, 2), 107 (M^+-H_2O, 63), 85 ($C_4H_5O_2^+$, 23), 80 ($C_5H_6N^+$, 100); HRMS: *m/z* calcd for $C_7H_9NO_2$ [M^+]: 125.0477; found: 125.0486.

Reaction with tiglic acid (**6b**): Yield: 262 mg (84%) as a mixture of **7b** and **8b** (60:40).

2-(Cyanomethyl)-2-methylbut-3-enoic acid (**7b**): oil; IR (KBr): υ= 3500-2700, 2251, 1861, 1779, 1693, 1416, 1281, 1136, 1000, 927 cm^{-1}; ^{1}H-NMR (500 MHz, MeOD): δ = 1.47 (s, 3H, CH_3-), 2.80 (d, *J* = 16.7 Hz, 1H, -C<u>H</u>HCN), 2.87 (d, *J* = 16.7 Hz, 1H, -CH<u>H</u>CN), 5.27 (d, *J* = 10.8 Hz, 1H, C<u>H</u>H=), 5.29 (d, *J* = 17.5 Hz, 1H, CH<u>H</u>=), 6.04 (dd, J_1 = 17.5 Hz, J_2 = 10.7 Hz, -CH=) ppm; ^{13}C-NMR (125 MHz, MeOD): δ = 21.0 (CH_3-), 25.5 (-<u>C</u>H$_2$CN), 47.5 (<u>C</u>-COOH), 114.6 (CN), 117.7 (CH_2=), 139 (CH=) 175.0 (COOH) ppm; MS: *m/z* (%) = 139 (M^+, 4), 121 (M^+-H_2O, 49), 112 (M^+-HCN, 37), 100 ($C_5H_9O_2^+$, 64), 99 ($C_5H_8O_2^+$, 93), 82 ($C_5H_6O^+$, 46), 81 ($C_5H_5O^+$, 33), 71 ($C_4H_7O^+$, 83), 68 ($C_5H_8^+$, 98), 67 ($C_5H_7^+$, 100); HRMS: *m/z* calcd for $C_7H_9NO_2$ [M^+]: 139.0633; found: 139.0674.

5-Cyano-2-methylpent-2-enoic acid (**8b**): oil; IR (KBr): υ= 3500-2700, 2251, 1861, 1779, 1693, 1416, 1281, 1136, 1000, 927 cm^{-1}; ^{1}H-NMR (500 MHz, MeOD): δ = 1.84 (s, 3H, CH_3-), 2.35 (m, 2H, -C<u>H</u>$_2$CH$_2$CN), 2.61 (m, 2H, -CH$_2$C<u>H</u>$_2$CN), 6.78 (m, 1H, -CH=) ppm. ^{13}C-NMR (125 MHz, MeOD): δ = 11.2 (CH_3-), 24.2 (-<u>C</u>H$_2$CN), 27.2 (-<u>C</u>H$_2$-C=), 118.2 (CN), 128.5 (<u>C</u>-COOH), 140.0 (CH=) 170.1 (COOH) ppm; MS: *m/z* (%) = 139 (M^+, 4), 121 (M^+-H_2O, 49), 112 (M^+-HCN, 37), 100 ($C_5H_9O_2^+$, 64), 99 ($C_5H_8O_2^+$, 93), 82 ($C_5H_6O^+$, 46), 81 ($C_5H_5O^+$, 33), 71 ($C_4H_7O^+$, 83), 68 ($C_5H_8^+$, 98), 67 ($C_5H_7^+$, 100); HRMS: *m/z* calcd for $C_7H_9NO_2$ [M^+]: 139.0633; found: 139.0674.

2-(Cyanomethyl)-3-methylbut-3-enoic acid (**7c**). From dimethylacrylic acid (**6c**, 225 mg); yield: 250 mg (80%); oil; IR (KBr): υ= 3500-2750, 2349, 1767, 1695, 1403, 1243, 978, 914, 870, 751, 720 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.85 (s, 3H, CH_3), 2.69 (dd, J_1 = 16.9 Hz, J_2 = 8.2 Hz, 1H, -C<u>H</u>HCN), 2.86 (dd, J_1 = 16.9 Hz, J_2 = 7.0 Hz, 1H, -CH<u>H</u>CN), 3.48 (t, *J* = 7.1 Hz, 1H, C<u>H</u>COOH), 5.09 (s, 1H, C<u>H</u>H=), 5.16 (s, 1H, CH<u>H</u>=) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.7 (<u>C</u>H$_2$CN), 20.2 (CH_3), 48.0 (<u>C</u>HCOOH), 117.1 (CH_2=), 117.4 (CN), 138.7 (CH_3-C), 175.7 (COOH) ppm; MS: m/z (%) = 139 (M^+, 12), 121 (M^+-H_2O, 10), 112 (M^+-HCN, 8), 107 (M^+-O_2, 19), 94 (M^+-CH_2CN, 30), 93 (M^+-H_2O-CO, 19), 82 ($C_5H_6O^+$, 17), 73 ($C_3H_7NO^+$, 100), 68 ($C_5H_8^+$, 38), 67 ($C_5H_7^+$, 66); HRMS: m/z calcd for $C_7H_9NO_2$ [M^+]: 139.0633; found: 139.0622.

3-(2-cyanoethyl)thiophene-2-carboxylic acid (**10**). From 3-methylthiophene-2-carboxylic acid (**9**, 320 mg); yield: 378 mg (57%); amber oil; IR (KBr): υ= 3400-2400, 2242, 1680, 1599, 1433, 1376, 1265, 1091, 825, 692 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3CN): δ = 2.74 (t, J = 7.1 Hz, 2H, CH_2CN), 3.30 (t, J = 7.0 Hz, C<u>H</u>$_2$CH$_2$CN), 7.12 (d, J = 5.1 Hz, 1H, C<u>H</u>CH-S), 7.62 (d, J = 5.0 Hz, 1H, CH-S) ppm; ^{13}C-NMR (100 MHz, CD_3CN): δ = 17.4 (<u>C</u>H$_2$CN), 25.9 (<u>C</u>H$_2$CH$_2$CN), 117.3 (CN), 129.0 (<u>C</u>HCH-S),

130.8 (CH-S), 131.1 (C-COOH), 146.5 (C-CH_2), 163.0 (COOH) ppm; MS: m/z (%) = 181 (M^+, 65), 154 (M^+-HCN, 63), 141 (M^+-CH_2CN, 100); HRMS: m/z calcd. for $C_8H_7NO_2S$ [M^+]: 181.0198; found: 181.0199.

2-(2-Cyanomethyl)-5-methylfuran-3-carboxylic acid (**12**). From 2,5-dimethylfuran-3-carboxylic acid (**11**, 315 mg); yield: 278 mg (70%); powder (m.p. 105-107ºC); IR (KBr): υ= 3500-2500, 2283, 1789, 1591, 1424, 1379, 1227, 1076, 851, 747 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H, CH_3), 2.74 (t, J = 7.5 Hz, 2H, CH_2CN), 3.34 (t, J = 7.4 Hz, 2H, CH_2CH_2CN), 6.30 (s, 1H, CH_{Ar}) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.4 (CH_3), 16.1 (CH_2CN), 24.1 (CH_2CH_2CN), 106.8 (CH_{Ar}), 115.0 (C-COOH), 152.2 (C-CH_3), 157.6 (C-CH_2-), 168.8 (COOH) ppm; MS: m/z (%) = 179 (M^+, 13), 152 (M^+-HCN, 17), 139 ($C_7H_7O_3^+$, 84), 118 ($C_8H_8N^+$, 29), 78 ($C_5H_2O^+$, 100); HRMS: m/z calcd. for $C_9H_9NO_3$ [M^+]: 179.0582; found: 179.0572.

4-Amino-2-phenylbutanoic acid (**5c**). The cyanoacid **4c** (3.79 mg, 2.16 mmol) in AcOH (15 mL) was hydrogenated at room temperature under 40 psi hydrogen atmosphere for 3 days and filtrated through Celite®. After evaporation of the filtrate the crude product **5c** (380 mg, >99%) was obtained. No further purification was needed. IR (KBr): υ= 3500-2100, 3013, 1655, 1508, 1477, 1350, 1293, 1039, 721, 637 cm^{-1}; ^{1}H-NMR (300 MHz, MeOD): δ = 2.02 (bs, 1H, CH-CHH), 2.27 (bs, 1H, CH-CHH), 2.80 (bs, 1H, CHH-NH_2), 2.91 (bs, 1H, CHH-NH_2), 3.55 (bs, 1H, CH-COOH), 7.31 (m, 5H, Ph-H) ppm; ^{13}C-NMR (75 MHz, MeOD): δ = 32.8 (CH-CH_2), 39.2 (CH_2-NH_2), 53.2 (CH-COOH), 127.9 (CH_{Ar}), 129.6 (CH_{Ar}), 129.7 (CH_{Ar}), 142.0 (C_{Ar}), 178.1 (COOH) ppm; MS: m/z (%) = 179 (M^+, 2), 161 (M^+-H_2O, 53), 117 ($C_9H_9^+$, 100), 91 ($C_7H_7^+$, 63); HRMS: m/z calcd. for $C_{10}H_{13}NO_2$ [M^+]: 179.0946; found: 179.0956.

Acknowledgements

The present research has been financed by DGCYT (CTQ2005-07562-C04-01/BQU) and by the Agencia Valenciana de Ciencia y Tecnología (GV06/050, GVACOMP2007-080, REVIV:QUIMICA 863/2007).

References and Notes

1. (a) McGeer, P. L.; McGeer, E. G. In *Basic Neurochemistry, 4th ed*.; Seigel, G.; Agranoff, B.; Albers, R. W.; Molinof, P., Eds.; Raven: New York, **1989**; (b) Hansen, J. J.; Krogsgaardlarsen, P. Structural, Conformational and Sterochemical requirements of Central Excitatory Amino-Acid Receptors. *Med. Res. Rev.* **1990**, *10*, 55-94.
2. (a) Lindquist, C. E. L.; Birnir, B. Graded response to GABA by native extrasynaptic GABA(A) receptors. *J. Neurochem*. **2006**, *97*, 1349-1356; (b) Sinclair, J.; Granfeldt, D.; Pihl, J.; Millingen, M.; Lincoln, P.; Farre, C.; Peterson, L.; Orwar, O. A biohybrid dynamic random access memory. *J. Am. Chem. Soc*. **2006**, *128*, 5109-5113.

3. Suman-Chauhman, N.; Webdale, L.; Hill, D. R.; Woodruff, G. N. Characterization of [3H]Gabapentin Binding to a Novel Site in Rat-Brain – Homogenate Binding-Studies. *Eur. J. Pharmacol. Mol. Pharmacol. Sect.* **1993**, *244*, 293-301.
4. See for example: (a) Burgos-Lepley, C. E.; Thompson, L. R.; Kneen, C. O.; Osborne, S. A.; Bryans, J. S.; Capiris, T.; Suman-Chauhan, N.; Dooley, D. J.; Donovan, C. M.; Field, M. J.; Vartanian, M. G.; Kinsora, J. J.; Lotarski, S. M.; El-Kattan, A.; Walters, K.; Cherukury, M.; Taylor, C. P.; Wustrow, D. J.; Schwarz, J. B. Carboylate bioisosteres of Gabapentin. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2333-2336; (b) Denis, J-N.; Tchertchian, S.; Tomassini, A.; Vallée, Y. The reaction of propiolate acetylides with nitrones. Synthesis of γ-amino-α,β-ethyleninc acid derivatives. *Tetrahedron Lett*. **1997**, *38*, 5503-5506; (c) Azam, S.; D'Souza, A. A.; Wyatt, P. B. J. Enantioselective synthesis of 2-substituted-4-aminobutanoic acid (GABA) analogues via cyanomethyl methylation of chiral enolates. *J. Chem. Soc. Perkin Trans. I* **1996**, 621-627. (d) Deng, J.; Duan, Z.C.; Huang, J.D.; Hu, X.P.; Wang, D.Y.; Yu, S.B.; Xu, X.F.; Zheng, Z. Rh-catalyzed asymmetric hydrogenation of gamma-phthalimido-substituted alpha,beta-unsaturated carboxylic acid esters: An efficient enantioselective synthesis of beta-aryl-gamma-amino acids. *Org. Lett.* **2007**, *9*, 4825-4828. (e) Winkler, M.; Knall, A.C.; Kulterer, M.R.; Klempier, N. Nitrilases catalyze key step to conformationally constrained GABA analogous gamma-amino acids in high optical purity. *J. Org Chem.* **2007**, *72*, 7423-7426. (f) Ordonez, M.; Cativiela, C. Stereoselective synthesis of gamma-amino acids. *Tetrahedron: Asymmetry* **2007**, *18*, 3-99.
5. See for example: (a) Martin, C. J.; Rawson, D. J.; Williams, J. M. J. The preparation of enenatiomerically enriched γ-aminoacids (GABAs) using palladium catalyzed allylic substitution. *Tetrahedron: Asymmetry* **1998**, *9*, 3723-3730; (b) Dryanska, V.; Pashkuleva, I. A simple and efficient synthesis of gamma-aminobutyric acid (GABA). *Org. Prep. Proced. Int.* **1999**, *31*, 232-236; (c) Dryanska, V.; Pashkuleva, I.; Angelov, V. A convenient synthesis of threo-4-amino-3, 4-diphenylbutanoic acid and its derivatives. *J. Chem. Res.-S* **2003**, 89-90. (d) Kohler, F.; Gais, H.J.; Raabe, G. Asymmetric synthesis of highly substituted gamma-amino acids from allyltitanium sulfoximines. *Org. Lett.* **2007**, *9*, 1231-1234.
6. (a) Calmès, M.; Escale, F.; Martinez, J. Synthesis of N-Boc-(R)-α-phenyl-γ-aminobutyric acid using and in situ diastereoselective protonation strategy. *Tetrahedron: Asymmetry* **2002**, *13*, 293-296; (b) Camps, P.; Muñoz-Torrero, D.; Sánchez, L. Stereoselective synthesis of both enantiomers of N-Boc- α-phenyl-γ-aminobutyric acids. *Tetrahedron: Asymmetry* **2004**, *15*, 311-321. (c) Bergner, I.; Opatz, T. alpha-Aminonitriles and alpha-(alkylideneamino)nitriles can serve as readily available alpha-aminocarbanion equivalents. Their conjugate addition to alpha,beta-unsaturated esters followed by reduction furnishes polysubstituted gamma-amino acid esters in moderate to high yield. *Synthesis* **2007**, 918-928. (d) Amruta Reddy, P.; Hsiang, B.C.H.; Latifi, T.N.; Hill, M.W.; Woodward, K.E.; Rothman, S.M.; Ferrendelli, J.A.; Covey, D.F. 3,3-Dialkyl- and 3-alkyl-3-benzyl-substituted 2-pyrrolidinones: a new class of anticonvulsant agents. *J. Med. Chem*. **1996**, *39*, 1898-1906.
7. (a) Brun, E.M.; Gil, S.; Mestres, R.; Parra, M. Lithium enediolates and dienediolates of carboxylic acids in synthesis: Alkylation with secondary halides. *Tetrahedron.* **1998**, *54*, 15305-15320; (b) Aurell, M. J.; Gil, S.; Mestres, R.; Parra, M.; Parra, L. Alkylation of lithium dienediolates of

butenoic acids. Regioselectivity effects of structure and leaving group of the alkylating agent. *Tetrahedron* **1998**, *54*, 4357-4366.

8. Gil, S; Parra, M; Rodriguez, P. A simple synthesis of γ-aminoacids. *Tetrahedron Lett.* **2007**, *48*, 3451-3453.
9. Brun, E.M.; Gil, S.; Parra, M. Enantioselective alpha-alkylation of unsaturated carboxylic acids using a chiral lithium amide. *Tetrahedron: Asymmetry* **2001**, *12*, 915-921.
10. (a) Thomson, C. M. In *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, FL, **1994**; pp. 88-129; (b) Gil, S.; Parra, M. Dienediolates of carboxylic acids in synthesis. Recent advances. *Curr. Org. Chem.* **2002**, *6*, 283-302; (c) Gil, S.; Parra, M. Reactivity control of dianions of carboxylic acids. Synthetic applications. *Recent Res. Devel. Org. Chem.* **2002**, *6*, 449-481.
11. Clayden, I. In *Organolithiums: selectivity for synthesis*; Pergamon Press: Oxford, **2002**; p. 73.
12. Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. Enantioselective Aldol and Michael Additions of Achiral Enolates in the presence of chiral lithium amides and amines. *Synthesis* **1993**, 1271-1290.
13. (a) Streitwieser, A.; Husemann, M.; Kim, Y-J. Aggregation and reactivity of the dilithium and dicesium N-diolates of 1-naphthyl acetic acid. *J. Org. Chem.* **2003**, *68*, 7937-7942; (b) Eames, J.; Suggate, M. J. Recent developments in the transfer of chirality within enolate alkylation reactions. *Angew. Chem. Int. Ed.* **2005**, *44*, 186-189; (c) Sott, R.; Granader, J.; Hilmersson, G. Solvent-dependent mixed complex formation –NMR studies and asymmetric addition reactions of lithiumacetonitrile to benzaldehyde mediated by chiral lithium amides. *Chem. Eur. J.* **2002**, *8*, 2081-2087; (d) Sotoca, E.; Bouillon, J. P.; Gil, S.; Parra, M.; Portella, C. Reaction of lithium enediolates with perfluoroketene dithioacetals. Synthesis of α-trifluoromethyl γ-dicarboxylic acid derivatives. *Tetrahedron* **2005**, *61*, 4395-4402.
14. (a) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. Dienediolates of α,β-unsaturated carboxylic acids in synthesis: A new synthetic method to 2-pyridones. *Synlett.* **1999**, 1088-1090; (b) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. A new synthetic method to 2-pyridones. *Synthesis* **2000**, 273-280; (c) Brun, E. M.; Gil, S.; Parra, M. New approach to condensed pyrid-2-ones. *Arkivoc* **2002**, *X*, 80-89.
15. (a) Brun, E. M.; Casades, I.; Gil, S.; Mestres, R.; Parra, M. New conditions for the generation of dianions of carboxylic acids. *Tetrahedron Lett.* **1998**, *39*, 5443-5446; (b) Gil, S.; Torres, M.; Ortúzar, N.; Wincewicz, R.; Parra, M. Eficient addition of acid enediolates to epoxides. *Eur. J. Org. Chem.* **2004**, 2160-2165.
16. Enders, D; Gröbner, R.; Raaba, G. Enantioselective synthesis of 2-substituted 5-, 6- and 7-membered lactams via α-alkylation of their chiral N-dialkylamino derivatives. *Synthesis* **1996**, 941-948.
17. Murakata, M.; Yasukata, T.; Aoki, T.; Nakajima, M.; Koga, K. Stereoselective reactions. 30. Enantioselective alkylation of the lithium enolates of 6-membered cyclic ketones using tetradentated chiral amines in the presence of lithium bromide. *Tetrahedron* **1998**, *54*, 2449-2458.
18. Domingo, L.R.; Gil, S.; Parra, M.; Saez, J.A.; Torres, M. Experimental and theoretical investigations for the tandem alkvlation-isomerization reactions between unsaturated carboxylic acids and allyl halides. *Tetrahedron* **2003**, *59*, 6223-6239.

19. (a) O'Brien, P. Recent advances in asymmetric synthesis using chiral lithium amide bases. *J. Chem. Soc. Perkin Trans I* **1998**, 1439-1457; (b) Duguet, N.; Harrison-Marchand, A.; Maddamno, J'y; Tomioka, K. Enantioselective conjugate addition of a lithium ester enolate catalyzed by chiral lithium amides. *Org. Lett.* **2006**, *8*, 5745-5748; (c) Matsubara, H.; Maeda, L.; Sugiyama, H.; Ryn, I. Chiral and achiral lithium amides having a fluorous ponytail: Preparation and evaluation as a recycling reagent for lithium enolate generation. *Synthesis* **2007**, 2901-2912.
20. Matsuo, J.-i; Koga, K. Enantioselective alpha-alkylation of phenylacetic acid using a chiral bidentate lithium amide as a chiral auxiliary. *Chem. Pharm. Bull*. **1997**, *45*, 2122-2124.
21. (a) Parra, M.; Sotoca, E.; Gil, S. A convenient generation of acetic acid dianion. *Eur. J. Org. Chem.* **2003**, 1386-1388; (b) Newton, R.; Marsden, S. P. Efficient synthesis of quaternary alpha-hydroxy acids by alkylation of alpha-ketoamide-derived dienediolates. *Synthesis* **2005**, 3263-3270.

Sample Availability: Samples of the compounds **4c**, **4d**, **7c**, **7b** and **12** are available from the authors.