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A simple synthesis of γ-aminoacids

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Dedicated to Professor Julio Gonzalez Urones on the occasion of his 65th birthday

Abstract—The addition of dianions of carboxylic acids to bromoacetonitrile, leads, in good yields, to the corresponding γ-cyanoacids that give γ-aminoacids on hydrogenation. This two-step methodology improves the results previously described.

γ-Aminoacids is a family of compounds exhibiting important biological functions, for example, γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the mammalian central nervous system.[1–4]

Those facts have created an important demand for the synthesis of γ-aminoacids.[5] In particular, those analogues bearing a phenyl group in the α, β or γ positions have received much attention.[6]

Some authors have developed a stereoselective synthesis of these compounds with a deracemization strategy from a chiral ester. This ester is obtained from a racemic acid via protection as a methyl ester, alkylation of the corresponding enolate, hydrolysis (described combined yields 60–70%) and a new esterification with a chiral auxiliary. One of the chiral auxiliaries with best results is (*R*)-pantolactone.[7]

In this Letter, we wish to report a new approach to the synthesis of racemic γ-amino acids by applying the carboxylic acid dianion methodology. This allows a two-step reduction of the synthetic strategies described above. Carboxylic acids are synthetically useful building blocks because, after double deprotonation, they afford enediolates that react with several electrophiles under the appropriate conditions.[8] Lithium dialkylamides are the most common bases for the generation of their lithium enediolates[8,9] due to their strength and low nucleophilicity combined with their solubility in non-polar solvents.[9,10] It is well established that lithium enolates exist as complex ion pair aggregates in these solvents, whose metal centre may be coordinated to solvent molecules or to other chelating ligands, such as the amines resulting from a deprotonation of the acid by the lithium amide. The data available so far confirm the complexity present in these aggregated reactive species, whose reactivity and selectivity can be influenced by many different factors[8,10,11] and an optimization study for each new electrophile is required.

We wish to describe a simple method to obtain γ-amino acids in two steps: addition of enediolates of carboxylic acids to bromoacetonitrile followed by catalytic hydrogenation of the nitrile group (Scheme 1).

Our group has a long experience in the addition of carboxylic acids to alkyl halides[12] and nitriles.[13] The former is a fast reaction which can be completed at low temperature, whereas the latter is a reversible process that requires a final exergonic step for the reaction to progress to completion. Despite having both a nitrile and a halide in the same electrophile, we discovered that optimizing the reaction time and the amount of amine enabled the reaction to generate the alkylated product.

The dianion is generated by treating the corresponding acid with lithium dialkylamine. After addition of the bromoacetonitrile, 24 h at room temperature has proven to be the best reaction conditions.[14] The corresponding yields are provided in Table 1.

Keywords: GABA; γ-Aminoacids; Bromoacetonitrile; Enediolate; Regioselectivity.
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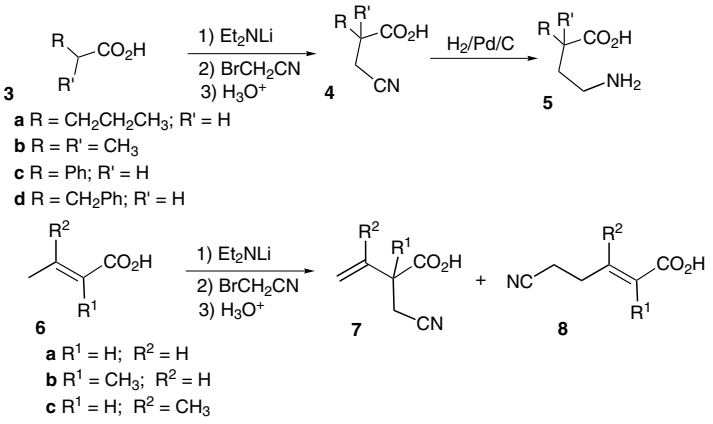
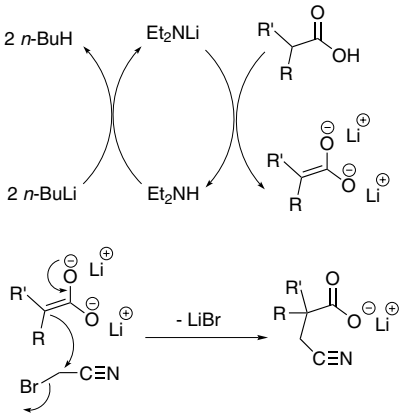


Scheme 1. Reaction of bromoacetonitrile with saturated and unsaturated carboxylic acids.

Table 1. Addition of dianions of carboxylic acids to bromoacetonitrile

Entry	Acid	Eq. Amine	Yield (%)	Regioselectivity	
				α (%)	γ (%)
1	**3a**	2	0		
2	**3a**	0.5	71		
3	**3b**	0.5	42		
4	**3c**	0.5	78		
5	**3d**	2	67		
6	**3d**	0.5	97		
7	**6a**	0.5	73	51	49
8	**6b**	2	77	40	60
9	**6b**	0.5	84	60	40
10	**6c**	2	69	100	0
11	**6c**	0.5	80	100	0



Scheme 2. Catalytic cycle for dianion generation and the alkylation mechanism.

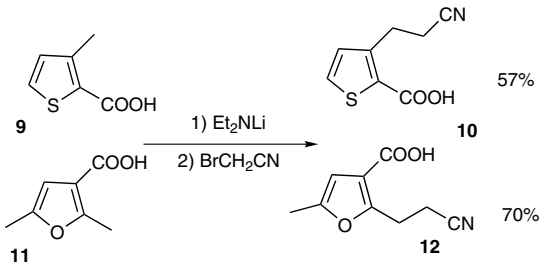
Previous studies led us to develop a substoichiometric lithium amide procedure for the generation of dianions of carboxylic acids which, in some cases, improved the yield and selectivity of the reaction. We optimized a complete generation of dianions of carboxylic acids by using an equimolecular amount 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 (Scheme 2) is possible as a carboxylate and the corresponding dianion can be held together without self-condensation.[15] This is the advantage that enediolates offer over simple enolates, especially those derived from esters.

We tried with several amines, namely, diethylamine, diisopropylamine, cyclohexyl isopropylamine and 1,3,3-trimethyl-6-azabicycle[3.2.1.]octane, but diethylamine proved to be the most efficient for this reaction. Table 1 displays that, 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 reprotonation by the amine while others do not. We think that this is the crucial factor to determine whether yields are higher with sub-stoichiometric or 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, as mentioned above.

Products are isolated in high purity after a work-up separation of neutral and acid fractions. Small variable amounts of starting acid are found in some cases in the acid fraction.

Usually, products **4** are efficiently reduced to γ-amino acids **5** by catalytic hydrogenation[5c] in quantitative yields, and their spectroscopical data agree with those described in the literature.[7,16] A higher pressure and a longer reaction time are required for **4a.** This methodology improves the results described to date, which requires at least two additional steps: protection and deprotection of the carboxyl group.

We have extended this methodology to α,β-unsaturated carboxylic acids, whose double deprotonation led to dienediolates that behave as ambident nucleophiles through their α or γ carbon atoms.[8] Although the α attack predominates for irreversible reactions, strong deviations are observed in alkylation reactions.[12] Results with bromoacetonitrile are summarized in Table 1. Only α-adducts (Products **7**) are observed with the addition of dimethylacrylic acid **6c**. The regioselectivity has not been controlled for the remaining acids and mixtures



Scheme 3. Reaction of bromoacetonitrile with *o*-methyl aromatic acids.

of α, and γ adducts were observed. It is worth noting that the regioselectivity is modified according to the progress of the reaction. This phenomenon is explained by the presence of LiBr; generated as the reaction progresses (Scheme 2).[17]

The method can be extended to *o*-methyl aromatic acids, as seen in Scheme 3. Acids **10** and **12** are obtained in 57% and 70% yields, respectively. Unfortunately, reactions with *o*-toluic and 2-methylnicotinic acids, under different conditions, mainly led to the starting acid.

In conclusion, we describe a general procedure for the addition of dianions of carboxylic acids to bromoacetonitrile. This methodology is a new approach from saturated carboxylic acids to the synthesis of γ-aminoacids that are obtained in higher yields (around 75%) than those described.[7] The method can be extended to unsaturated carboxylic acids.

Acknowledgements

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References and notes

1. (a) McGeer, P. L.; McGeer, E. G. In *Basic Neurochemistry*, 4th ed.; Seigel, G., Agranoff, F., Albers, R. W., Molinof, P., Eds.; Raven: New York, 1989; (b) Krogsqaardlarsen, P. *Compr. Med. Chem.* **1990**, *3*, 493.
2. (a) Lindquist, C. E. L.; Birnir, B. *J. Neurochem.* **2006**, *97*, 1349; (b) Sinclair, J.; Granfeldt, D.; Pihl, J.; Millingen, M.; Lincoln, P.; Farre, C.; Peterson, L.; Orwar, O. *J. Am. Chem. Soc.* **2006**, *128*, 5109.
3. (a) Delgado-Escueta, A. V.; Ward, A. A., Jr.; Woodbury, D. M.; Parter, R. J. *Basic Mechanisms of the Epilepsies*; Raven Press: New York, 1986; pp 365–378; (b) Silverman, R. B.; Andruszkiewicz, R.; Nanavati, S. M.; Taylor, C. P.; Vartanian, M. G. *J. Med. Chem.* **1991**, *34*, 2295; (c) Taylor, C. P.; Vartanian, M. G.; Andruszkiewicz, R.; Silverman, R. B. *Epilepsy Res.* **1992**, *11*, 103.
4. Suman-Chauhan, N.; Webdale, L.; Hill, D. R.; Woodruff, G. N. *Eur. J. Pharmacol., Mol. Pharmacol. Sect.* **1993**, *244*, 293.
5. 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. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2333; (b) Denis, J.-N.; Tchertchian, S.; Tomassini, A.; Vallée, Y. *Tetrahedron Lett.* **1997**, *38*, 5503; (c) Azam, S.; D'Souza, A. A.; Wyatt, P. B. J. *Chem. Soc., Perkin Trans. 1* **1996**, 621.
6. See for example: (a) Martin, C. J.; Rawson, D. J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3723; (b) Dryonska, V.; Pasnkuleva, I. *Org. Prep. Proced. Int.* **1999**, *31*, 232.
7. (a) Calmès, M.; Escale, F.; Martinez, J. *Tetrahedron: Asymmetry* **2002**, *13*, 293; (b) Camps, P.; Muñoz-Torrero, D.; Sánchez, L. *Tetrahedron: Asymmetry* **2004**, *15*, 311.
8. (a) Thomson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton (FL), 1994; pp 88–129; (b) Gil, S.; Parra, M. *Curr. Org. Chem.* **2002**, *6*, 283; (c) Gil, S.; Parra, M. *Recent Res. Dev. Org. Chem.* **2002**, *6*, 449.
9. Clayden, I. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: Oxford, 2002; pp 73.
10. Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopedhyay, T.; Simon, M.; Seebach, D. *Synthesis* **1993**, 1271.
11. (a) Streitwieser, A.; Husemann, M.; Kim, Y.-J. *J. Org. Chem.* **2003**, *68*, 7937; (b) Eames, J.; Suggate, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 186; (c) Scott, R.; Granader, J.; Hilmersson, G. *Chem. Eur. J.* **2002**, *8*, 2081; (d) Sotoca, E.; Bouillon, J. P.; Gil, S.; Parra, M.; Portella, C. *Tetrahedron* **2005**, *61*, 4395.
12. (a) Aurell, M. J.; Gil, S.; Mestres, R.; Parra, M.; Parra, L. *Tetrahedron* **1998**, *54*, 4357; (b) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Tetrahedron* **1998**, *54*, 15305; (c) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Synthesis* **2000**, 1160; (d) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Synlett* **2001**, 156.
13. (a) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Synlett* **1999**, 1088; (b) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Synthesis* **2000**, 273; (c) Brun, E. M.; Gil, S.; Parra, M. *Arkivoc* **2002**, 80.
14. *General procedure*: *n*-BuLi (1.6 M in hexane, 5 mmol) was introduced with stirring into a reaction flask that has been purged. Hexane was evaporated under vacuum, the flask cooled at −78 °C and then THF (2 mL) was added to redissolve the BuLi. Diethylamine (1 mmol) was added at −78 °C. The mixture was stirred for 15 min at 0 °C. The acid (2.25 mmol) in THF (2 mL) was added slowly at −78 °C. After 30 min at 0 °C usually a clear solution of the dianion was formed. Bromoacetonitrile (2.25 mmol) in THF (2 mL) was added slowly at −78 °C. 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 × 15 mL). The aqueous phase was acidified with concd HCl to pH 1 and then extracted with EtOAc (3 × 15 mL) and the combined extracts were dried over anhyd $MgSO_4$. After evaporation of the solvent, the cyanoacids are obtained pure enough for the following hydrogenation step.
15. (a) Brun, E. M.; Casades, I.; Gil, S.; Mestres, R.; Parra, M. *Tetrahedron Lett.* **1998**, *39*, 5443; (b) Gil, S.; Torres, M.; Ortúzar, N.; Wincewicz, R.; Parra, M. *Eur. J. Org. Chem.* **2004**, 2160.
16. Enders, D.; Gröbner, R.; Raabe, G.; Runsink, J. *Synthesis* **1996**, 941.
17. (a) Murakata, M.; Yasukata, T.; Aoki, T.; Nakajima, M.; Koga, K. *Tetrahedron* **1998**, *54*, 2449; (b) Brun, E. M.; Gil, S.; Parra, M. *Tetrahedron: Asymmetry* **2001**, *12*, 915.