Pergamon

Tetrahedron Letters, Vol. 38, No. 25, pp. 4501-4502, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00913-1

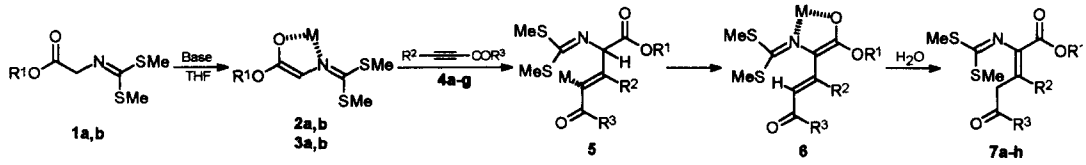
Reaction of N-[Bis(methylthio)methylene]glycinates with Electron Deficient Alkynes. Synthesis of (*Z*)-α,β-Didehydroglutamic Acid Derivatives

Carlos Alvarez-Ibarra*, Aurelio G. Csákÿ, Elena Martín Ortega, M. Jesús de la Morena and M. Luz Quiroga

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense. 28040 - Madrid

Abstract: The addition of either the alkaline enolates of the glycinates **1** or their naked enolates to electron defficient alkynes allows for the synthesis of substituted (*Z*)-α,β-didehydroglutamic acid derivatives **7** *via* a Michael addition /1,3-prototropic rearrangement sequence.

α,β-Didehydroamino acids constitute a relevant subclass within non proteinogenic amino acids, which include peptidic antibiotics, natural products and key intermediates in the synthesis of non natural α-amino acids.[1] The protection of the nitrogen atom in these compounds as N-diphenylmethylene or N-[bis(methylthio)methylene] derivatives has proven of use from a synthetic standpoint.[2] On the other hand, conformationally restricted glutamic acid derivatives are currently being used in the treatment of Altzheimer's desease, epilepsy and stroke.[3] We report herein the reaction of the alkaline enolates **2** (M = Li, K) and of the naked anions **3** (M = :) derived from the glycinates[4] **1** with the π-defficient alkynes **4**, with obtention of the α,β-didehydroglutamic acid derivatives **7** *via* a Michael addition/1,3-prototropic rearrangement sequence (Scheme 1, Table 1).



Scheme 1

Deprotonation of ester **1a** with KO^{t}Bu, LDA, or BuLi followed by reaction with ethyl propiolate (**4a**) (entries 1 - 3) gave compound **7a**, which was obtained as a single isomer with a *Z* geometry in the C=C bond.[5] The same stereochemical result was obtained in the reactions of ester **1b** with **4a** (entry 4) and in the reactions of either **1a** or **1b** with the ethynylketones **4b-e** (entries 5 - 8). However, no reaction took place between the alkaline enolates **2** (M = Li, K) and the β-substituted alkynes **4f,g**. This could be overcome by the reaction of alkynes **4f,g** with the naked anions **3** (M = :), which were generated either by deprotonation of **1** with the phosphazene P4-^{t}Bu base[6] (entries 10, 12) or by treatment of the potassium enolates **2** (M = K) with 18-crown-6

(entries 9, 11). Compounds **7g,h** were also obtained as single *Z* isomers.[5]

Table 1. Addition Reaction of Glycinates **1** with Alkynes **4**[a]

No.	1	R^1	4	R^2	R^3	Base	7 (%)[b]
1	**1a**	^{t}Bu	**4a**	H	OEt	KO^{t}Bu	**7a** (85)
2	**1a**	^{t}Bu	**4a**	H	OEt	LDA	**7a** (80)
3	**1a**	^{t}Bu	**4a**	H	OEt	BuLi	**7a** (80)
4	**1b**	Et	**4a**	H	OEt	KO^{t}Bu	**7b** (85)
5	**1a**	^{t}Bu	**4b**	H	C_6H_5	KO^{t}Bu	**7c** (80)
6	**1b**	Et	**4c**	H	p-MeO-C_6H_5	KO^{t}Bu	**7d** (85)
7	**1b**	Et	**4d**	H	p-Br-C_6H_5	KO^{t}Bu	**7e** (75)
8	**1a**	^{t}Bu	**4e**	H	CH_3	KO^{t}Bu	**7f** (50)
9	**1a**	^{t}Bu	**4f**	CH_3	OEt	KO^{t}Bu/18-crown-6	**7g** (80)
10	**1a**	^{t}Bu	**4f**	CH_3	OEt	P4-^{t}Bu	**7g** (60)
11	**1b**	Et	**4g**	Ph	OEt	KO^{t}Bu/18-crown-6	**7h** (75)
12	**1b**	Et	**4g**	Ph	OEt	P4-^{t}Bu	**7h** (55)

(a) THF, -78°C, 15 min. (b) Pure isolated yields.

It is worth mentioning that no products arising from protonation of intermediate **5** or α-protonation of **6** were detected.

In conclusion, the addition of either the alkaline enolates of the glycinates **1** or their naked enolates to electron defficient alkynes should be considered a new reaction which allows for the synthesis of a wide variety of substituted α,β-didehydroglutamic acid derivatives, with anticipated utility as pharmacologically active compounds. This widens the scope of previously published procedures for the synthesis of α,β-didehydroamino acid derivatives.

Acknowledgements: The Dirección General de Investigación Científica y Técnica (Project PB93-0025) is gratefully acknowledged for finantial support. RMN and MS Services of UCM are also acknowledged.

References and Notes:

1. See for example: (a) Noda, K.; Shimohigashi, Y.; Izumya, N. in *The Peptides*, Academic Press: New York, 1983, Vol. 5, p. 285. (b) Schmidt, U.; Liberknecht, A.; Wild, J. *Synthesis* **1988**, 159 - 172.
2. (a) Buñuel, E.; Cativiela, C.; Díaz de Villegas, M. D.; Jiménez, A. I. *Synlett* **1992**, 579 - 581. (b) Cativiela, C.; Díaz de Villegas, M. D. *Tetrahedron* **1993**, *49*, 497 - 506. (b) Rubio, A.; Ezquerra, J. *Tetrahedron Lett.* **1995**, *36*, 5823 - 5826. (c) Jonczyk, A.; Pakulski, Z. *Tetrahedron Lett.* **1996**, *37*, 8909 - 89012. (d) López, A.; Moreno-Mañas, M.; Pleixats, R.; Roglans,A.; Ezquerra, J.; Pedregal, C. *Tetrahedron* **1996**, *52*, 8365 - 8386.
3. (a) Bridges, R. J.; Geddes, J. W.; Monaghan, D. T.; Cotman, C. W. in *Excitatory Amino Acis in Health and Disease*; Lodge, D., Ed., Wiley: New York, 1988, p. 321. (b) Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith III, A. B. *J. Am. Chem. Soc.* **1996**, *118*, 3584 - 3590.
4. (a) Hoppe, D. *Angew Chem. Int. Ed.* **1975**, *14*, 424 - 426. (b) Hoppe, D.; Beckmann, L. *Lieb. Ann. Chem.* **1979**, 2066 - 2075.
5. Determined by comparison of the ^{1}H-RMN data with those of related compounds. See ref. 2b.
6. (a) Schwesinger, R.; Schlemper, H.. *Angew.Chem., Int. Ed. Engl.* **1987**, *26*, 1167 - 1169. (b) Pietzonka, T.; Seebach, D. *Chem. Ber.* **1991**, *124*, 1837 - 1843.

(*Received in UK* 8 *April* 1997; *accepted* 9 *May* 1997)