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Synthesis and Reactivity of β-Amino-α,β-unsaturated Oxa- and Thiazolines

Santos Fustero *, Mª Dolores Díaz

Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, 46010-Valencia, Spain

José Barluenga *, Enrique Aguilar

Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33012-Oviedo, Spain

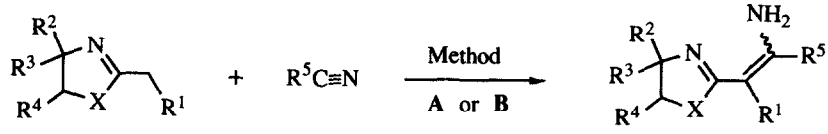
Key Words: Metalated heterocycles; oxa- and thiazolines; β-amino-α,β-unsaturated acid derivatives; β-aminoacids; alkylation-reduction

Abstract: A simple and efficient route to masked β-amino-α,β-unsaturated acids **3** by reaction of metalated oxa- and thiazolines with nitriles has been developed. The reactivity of **3** has also been explored.

β-Amino-α,β-unsaturated acid derivatives, particularly the β-amino-α,β-unsaturated esters, have attracted a great deal of attention because they are very important building blocks for the synthesis of natural products like alkaloids and antibiotics.[1] Their utility as intermediates in heterocyclic synthesis has also been described,[2] and they have been applied with success in asymmetric synthesis.[3] Simple β-amino-α,β-unsaturated esters are mostly synthesized either by condensation reaction of β-ketoesters with ammonia or amines[1a,b] or by nucleophilic addition of enolates of alkylesters to nitriles[4] or derivatives.[1c] While the first strategy presents, in some cases, the difficulty of the availability of the starting β-ketoester,[5] the second approach appears to be more logical, simple, and practical. However, the reported methods indicate that the success of the latter reaction is highly dependent on both the nature of the starting ester and the metal-enolate used. Thus, approaches that use magnesium enolates of *t*-butyl esters [4a] or modifications of the Blaise reaction [4b] appear to be the most efficient, although they normally require the use of an excess of ester to ensure a satisfactory chemical yield.

On the other hand, α-metalated heterocycles **1**, conveniently prepared from carboxylic acid derivatives,[6] are versatile nucleophiles used extensively in organic synthesis mainly by Meyers [6,7] (**1**, X=O,S) and Jones [8] (**1**, X=NR). Therefore, they can be a useful tool for the introduction of a masked carboxylic acid in the β-position of an enamine function. Herein, we wish to report our initial findings on the use of these systems as reagents for the synthesis of β-amino-α,β-unsaturated acid derivatives **3** by reaction of oxa- and thiazolines **1** with nitriles **2** (Scheme I).

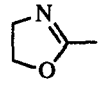
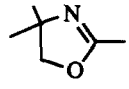
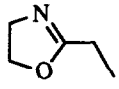
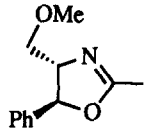
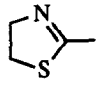
Metalation of **1** was performed by using *n*-butyl lithium or lithium diisopropylamide (LDA) in THF at -78 °C as previously described.[7] The resulting lithio salt was then allowed to react with 1.0 equivalent of nitrile **2**, and after stirring for several hours (-78 °C → r.t.) and an aqueous work-up, it afforded compounds **3** as the only products (Scheme I and Table). Pure compounds **3** were obtained after flash-chromatography, distillation, and/or recrystallization and show satisfactory microanalyses. The structure of **3** was ascertained on the basis of their spectroscopic data,[9] which indicate that they are isolated in the enamine form shown.



1 2 3

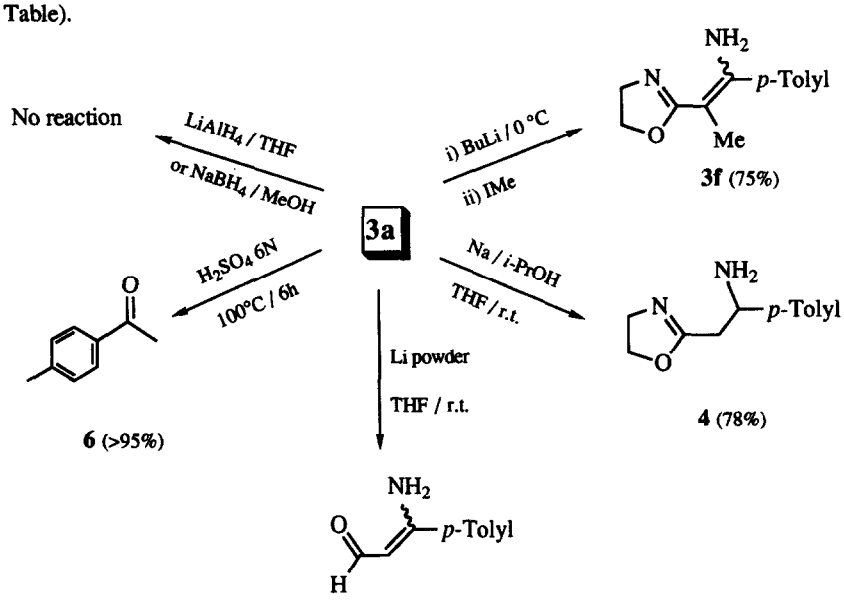
Scheme I

Table. Compounds **3** obtained by reaction of oxa- and thiazolines **1** and nitriles **2**.

1	Entry	R^5	Method [a]	3	Yield(%)	m.p.(°C) or b.p. (°C / Torr)
	1	*p*-Tolyl	A	**3a**	88	85-7
	2		B		84	
	3	$MeOCH_2$	A	**3b**	74	76-9 / 0.001
	4	Cyclopropyl	A	**3c**	78	72-4
	5	2-Furyl	A	**3d**	82	105-7
	6	*p*-Tolyl	A	**3e**	72	58-60
	7		B		89	
	8	*p*-Tolyl	A	**3f**	66	125-7
	9		B		77	
	10	*p*-Tolyl	A	**3g**	68	oil [d]
	11		B		78	
	12	Ph	A	**3h**	67 [e]	oil [d]
	13		B		95 [e]	

[a] Method **A**: LDA / THF / -78 °C ; Method **B**: *n*-BuLi / THF / -78 °C; [b] Yield of isolated product **3** based on **1**; [c] Melting points are uncorrected; [d] Purified by flash chromatography; [e] Yield of the crude product. During chromatographic purification of **3h** partial hydrolysis to the corresponding β-keto derivative was observed.

The process appears to be quite general both in **1** and **2**, does not require the use of an excess of reagents,[4] and gives rise **3** to high yields (see Table). It was further noted that the chemical yield was, in most cases, remarkably improved by the use of *n*-butyl lithium (method B, Table) as metalation agent instead of LDA (method A, Table).



Scheme II

The usefulness of this methodology in synthesis has been demonstrated in the preparation of β-amino-α,β-unsaturated aldehyde and β-amino acid derivatives by simple processes of reduction of **3**. Thus, for example, treatment of **3a** with an excess of lithium powder in THF at room temperature led directly to **5**, in a process that involves the one-pot selective reduction of the oxazoline ring to an aldehyde functionality.[6] Likewise, selective reduction of the enamine function can be achieved by reaction of **3a** with Na/*i*-PrOH in THF at 25 °C leading to **4** in 78% yield. However, as expected, no reduction was observed when compounds **3** were treated with complex hydrides like LAH or $NaBH_4$.[6]

On the other hand, acid hydrolysis of **3a** with 6N H_2SO_4 at 100 °C for 6 h. resulted, through a decarboxylation process, in the formation of the ketone **6** in more than 95% yield.

Finally, compounds **3** ($R^1 \neq H$) can alternatively be obtained via a metalation-alkylation sequence of **3** ($R^1=H$). Thus, deprotonation of **3a** using *n*-butyl lithium in THF at 0 °C followed by alkylation with methyl iodide gave rise **3f** to a 75% yield.

In summary, we describe a remarkably simple, high yielding route to masked β-amino-α,β-unsaturated acid derivatives **3** starting from oxa- and thiazolines **1**. Further studies about the reactivity and utility of systems **3** are in progress and will be reported in due course.

Acknowledgments

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References and Notes

1. See for example: (a) Mellillo, D.G.; Cvetovich, R.J.; Ryan, K.M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498-1504; (b) Hashiguchi, S.; Kawada, A.; Natsugari, H. *J. Chem. Soc. Perkin Trans. I*, **1991**, 2435-2444; (c) Fukuyama, T.; Yung, Y.M. *Tetrahedron Lett.* **1981**, *22*, 3759-3760; (d) Brunerie, P.; Célérier, J.; Petit, H.; Lhommet, G. *J. Heterocycl. Chem.* **1986**, *23*, 1183-1188.
2. (a) Wamhoff, H. in *Advances Heterocyclic Chemistry*; Katritzky, A.R.; Boulton, A.J., Eds.; Academic Press: New York **1985**; Vol. 38, pp 299-367; (b) Steglich, W.; Jeschke, R.; Busschmann, E. *Gazz. Chim. Ital.* **1986**, *116*, 361-372; (c) Boger, D.L.; Wysocki, R.J. *J. Org. Chem.* **1989**, *54*, 714-718.
3. (a) Lee, J.; Oya, S.; Snyder, J.K. *Tetrahedron Lett.* **1991**, *32*, 5899-5902; (b) Guingant, A.; Hammani, H. *Tetrahedron: Asymmetry* **1991**, *2(6)*, 411-414; (c) Huang, P.Q.; Zhou, W.S. *Tetrahedron: Asymmetry* **1991**, *2(9)*, 875-878.
4. (a) Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.* **1982**, *23*, 1597-1600; (b) Hannick, S.M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833-3835.
5. Conversely, β-amino-α,β -unsaturated esters have been used in several occasions as starting materials in the synthesis of β-ketoesters. See for example ref. 4b.
6. Recent reviews: (a) Reuman, M.; Meyers, A.I. *Tetrahedron* **1985**, *41*, 837-860; (b) Maryanoff, B.E. in *The Chemistry of Heterocyclic Compounds -Oxazoles*; Turchi, I.J. Ed.,; Interscience; New York, **1986**; Vol. 45, pp 963-1017.
7. See for example: (a) Lutowski, K.A.; Meyers, A.I. in *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: Orlando **1984**; Vol. 13, pp 213-274; (b) Meyers, A.I.; Durandetta, J.L. *J. Org. Chem.* **1975**, *40*, 2021-2025.
8. Jones, R.C.F.; Hirst, S.C.; Turner, I. *J. Chem. Soc. Perkin Trans. I* **1991**, 953-954 and literature cited therein.
9. Spectral data for compounds **3**: **3a**, $C_{12}H_{14}N_2O$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 2.4 (s, 3H), 4.0 (t, 2H, *J*=8.8 Hz), 4.2 (t, 2H, *J*=8.8 Hz), 4.9 (s, 1H), 6.8 (br s, 2H), 7.1-7.5 (m, 4H Ar); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 166.4 (C), 155.5 (C), 139.2 (C), 134.3 (C), 128.8 (CH), 125.4 (CH), 79.7 (CH), 65.1 (CH_2), 53.4 (CH_2), 20.6 (CH_3); MS *m/e*, 202 (M^+), 201 (100%). **3b**, $C_7H_{12}N_2O_2$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 3.3 (s, 3H), 3.9 (t, 2H, *J*=8.8 Hz), 4.0 (s, 3H), 4.2 (t, 2H, *J*=8.8 Hz), 4.5 (s, 1H) ; ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 166.0 (C), 153.3 (C), 79.3 (CH), 72.4 (CH_2), 65.3 (CH_2), 57.7 (CH_3), 54.0 (CH_2); MS *m/e*, 156 (M^+), 111 (100%). **3c**, $C_8H_{12}N_2O$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 0.7 (s, 2H), 0.8 (s, 2H), 3.9 (t, 2H, *J*=8.6 Hz), 4.1 (t, 2H, *J*=8.8 Hz), 4.5 (s, 1H), 6.2 (br s, 2H) ; ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 166.6 (C), 159.2 (C), 77.4 (CH), 65.1 (CH_2), 54.0 (CH_3), 15.4 (CH), 6.3 (2 x CH_2); MS *m/e*, 152 (M^+), 151 (100%).**3d**, $C_9H_{10}N_2O_2$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 3.9 (t, 2H, *J*=8.8 Hz), 4.2 (t, 2H, *J*=8.8 Hz), 5.2 (s, 1H), 6.5 (dd, 1H, *J*= 1.6 and 3.4 Hz), 6.6 (br s, 2H), 6.7 (d, 1H, *J*=3.4 Hz), 7.5 (d, 1H, *J*=1.6 Hz); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 166.6 (C), 149.9 (C), 144.4 (C), 142.9 (CH), 111.7 (CH), 107.8 (CH), 78.7 (CH), 65.5 (CH_2), 54.3 (CH_2); MS *m/e*, 178 (M^+, 100%). **3e**, $C_{14}H_{18}N_2O$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 1,3 (s, 6H), 2.3 (s, 3H), 3.8 (s, 2H), 4.8 (s, 1H), 7.2 (d, 2H Ar), 7.4 (d, 2H Ar); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 164.2 (C), 155.3 (C), 139.4 (C), 135.1 (C), 129.2 (CH), 125.7 (CH), 80.8 (CH), 66.6 (CH_2), 28.8 (CH_3), 21.0 (CH_3); MS *m/e*, 230 (M^+), 215 (100%). **3f** $C_{13}H_{16}N_2O$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 1.8 (s, 3H), 2.4 (s, 3H), 4.1 (t, 2H, *J*=8.8 Hz), 4.3 (t, 2H, *J*=8.8 Hz), 6.4 (br s, 2H), 7.1-7.3 (m, 4H Ar); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 168.5 (C), 152.8 (C), 138.1 (C), 136.0 (C), 128.8 (CH), 127.9 (CH), 87.3 (CH), 65.4 (CH_2), 54.4 (CH_2), 21.1 (CH_3), 14.3 (CH_3); MS *m/e*, 216 (M^+), 215 (100%). **3g**, $C_{20}H_{16}N_2O_2$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 2.3 (s, 3H), 3.3 (s, 3H), 3.5 (dq, 2H), 4.2 (m, 1H), 4.9 (s, 1H), 5.2 (d, 1H, *J*=7.5 Hz), 7.1-7.5 (m, 9H Ar); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 166.3 (C), 156.1 (C), 141.4 (C), 139.4 (C), 134.7 (C), 129.1 (CH), 128.3 (CH), 127.5 (CH), 125.6 (CH), 125.3 (CH), 81.4 (CH), 80.0 (CH), 75.1 (CH_2), 74.1 (CH), 58.8 (CH_3), 20.8 (CH_3); MS *m/e*, 322 (M^+), 277 (100%); $[\alpha]_D^{23}$ = +57.1 ° (*c* 1.5, $CHCl_3$). **3h**, $C_{11}H_{12}N_2S$. ^{1}HNMR ($CDCl_3$, TMS, 200 MHz) δ 3.2 (t, 2H), 4.3 (t, 2H), 5.1 (s, 1H), 6.8 (br s, 2H), 7.3-7.5 (m, 5H Ar); ^{13}CNMR ($CDCl_3$, TMS, 50 MHz) δ 166.8 (C), 153.4 (C), 139.0 (C), 129.3 (CH), 128.5 (CH), 125.9 (CH), 88.5 (CH), 64.3 (CH_2), 32.5 (CH_2); MS *m/e*, 204 (M^+), 203 (100%). **4**, $C_{12}H_{16}N_2O$ (oil): ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 2.1 (br s, 2H), 2.3 (s, 3H), 2.5 (d, 2H, *J*=7.3 Hz), 3.7 (t, 2H, *J*=9.3 Hz), 4.1 (t, 2H, *J*=9.3 Hz), 4.3 (t, 1H, *J*=7.0 Hz), 7.0-7.2 (dd, 4H Ar); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 166.3 (C), 141.7 (C), 136.6 (C), 128.9 (CH), 125.7 (CH), 66.8 (CH_2), 54.0 (CH_2), 52.5 (CH), 37.7 (CH_2), 20.7 (CH_3); MS *m/e*, 204 (M^+), 120 (100%). **5**, $C_{10}H_{11}NO$ (oil): ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 2.4 (s, 3H), 5.4 (d, 1H), 7.1 (br s, 2H), 7.2-7.5 (dd, 4H Ar), 9.3 (d, 1H); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 188.0 (CH), 162.3 (C), 141.4 (C), 133.2 (C), 129.5 (CH), 126.0 (CH), 95.2 (CH), 21.0 (CH_3); MS *m/e*, 161 (M^+), 160 (100%).

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