Pergamon

Tetrahedron Letters, Vol. 37, No. 27, pp. 4787-4790, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00936-7

Dilithiated (*E*)-*N*-Isobutyl-4-tosyl-2-butenamide: An Allyl Sulfone Dianion for the Regiospecific γ-Functionalization of Crotonamide Dianion

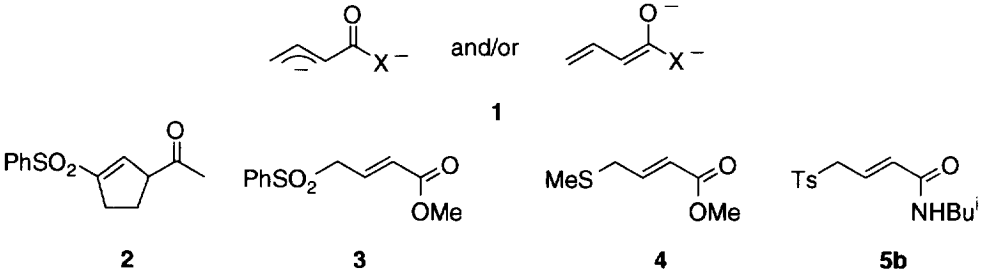
Francisco Caturla and Carmen Nájera*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

Abstract: (*E*)-*N*-Isobutyl-4-tosyl-2-butenamide (**5b**) (prepared from vinylacetic acid by stereoselective iodosulfonylation-dehydroiodination and further amidation) has been lithiated with two equiv of n-butyllithium at -78°C in the presence of DMPU leading to the corresponding allyl dianion **6**. This intermediate reacts with electrophiles (alkyl bromides, aldehydes and electrophilic olefins) regiospecific and stereoselectively at the γ-position to afford γ-substituted (*E*)-*N*-isobutyl-4-tosyl-2-butenamides **7**. Desulfonylation of compounds **7** occurs stereoselectively to provide (*E*)-β,γ-unsaturated amides **9**. This methodology has been applied to the synthesis of dienamides such as naturally occurring *N*-isobutyl-(2*E*,4*E*)-decadienamide (pellitorine). Copyright © 1996 Elsevier Science Ltd

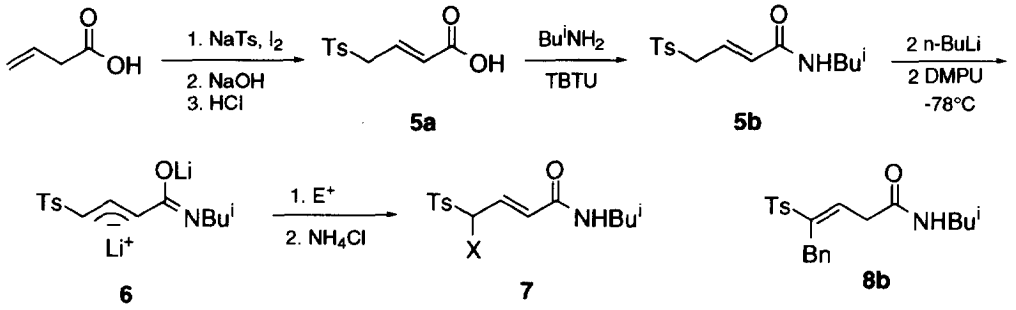
The control of the regioselectivity in the reaction of organometallic compounds derived from crotonic acid, esters or amides with electrophiles is still an unsolved problem. The reaction can take place at the α or γ-position depending on the type of crotonic acid derivative, the metal, the electrophile and the reaction conditions. The deconjugative α-alkylation of crotyl dianions **1** takes place mainly with alkyl halides and with carbonyl compounds at low temperatures.[1] In the case of carbonyl compounds[2] γ-adducts were mainly obtained under equilibrium conditions, whereas γ-arylation takes place with methoxy-substituted arynes as electrophiles.[3] Michael-type additions with α,β-unsaturated ketones occurred also mainly at the γ-position.[2a,4] On the other hand, the use of carbanions derived from allyl sulfones allows to direct the reaction with electrophiles at the α-position to the sulfone group. That means that the substitution at the γ-position of the crotonic systems by a sulfonyl group should be a good strategy to control the regioselectivity. Lansbury et al. found that in the case of γ-phenylsulfonyl substituted ketones, e.g. **2**,[5] mainly γ-alkylation occurred, but with dienoate anion derived from methyl γ-(phenylsulfonyl)-crotonoate (**3**)[5c] predominate α-alkylation was observed. Other sulfur-substituted derivatives such as methyl γ-(methylthio)crotonate (**4**)[6] underwent mainly α-alkylation.

In order to favour the reactivity of crotonic anions at the γ-position two strategies should be apropppiate, first to use a γ-tosyl-substituted derivative and second a *N*-monoalkylated amide to diminish the electron-atracting effect of the carboxamide group at the α-position after deprotonation. We have found that the dianion derived from (*E*)-*N*-isobutyl-4-tosyl-2-butenamide (**5b**) reacts with different type of electrophiles with total regioselectivity at the γ-position with respect to the amide, and therefore can be used for the stereoselective synthesis of β,γ-unsaturated amides and 2,4-dienamides.



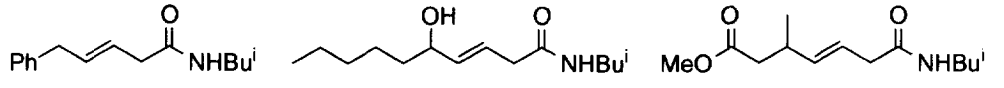
1 **2** **3** **4** **5b**

Starting amide **5b** was prepared from 3-butenoic acid,[7] which by iodosulfonylation with sodium *p*-toluenesulfinate and iodine in methanol followed by *in situ* dehydroiodination with 0.5M sodium hydroxide[8] and extractive acidification afforded steroselectively[11] (*E*)-4-tosyl-2-butenoic acid (**5a**)[12] in 70% overall yield. This acid was transformed into amide **5b** by treatment with oxalyl chloride and further reaction with isobutylamine or by amidation using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU)[13] in 50 or 80% yield, respectively. Treatment of amide **5b** with 2 equiv of n-butyllithium in the presence of *N,N'*-dimethylpropyleneurea (DMPU) at -78°C in THF for 15 min resulted in formation of the corresponding dianion **6**,[14] which reacted stereoselectively at the γ-position with different electrophiles to provide compounds **7** with *E*-configuration (Scheme 1 and Table 1). The deuterolysis of dianion **6** was carried out with monodeuterated methanol to yield compound **7a** in 80% yield and 75% of deuterium incorporation (300 MHz ^{1}H-NMR). The alkylation with benzyl bromide and *tert*-butyl bromoacetate was quenched at -60°C to afford alkylated products **7b** and **7c** in 55 and 72% yield, respectively (Table 1, entries 2 and 3) In the case of **7b** a 13% of isomerized compound **8b** (Scheme 1) was also obtained. When aldehydes were used as electrophiles the corresponding mixture of *erythro/threo*[15] diastereomeric β-hydroxy sulfones **7d-g** with *E*-configuration were isolated, but in the case of pivalaldehyde only the *erythro* isomer was obtained (Table 1, entry 5). Michael adducts **7h** and **7i** (Table 1, entries 8 and 9) derived from methyl crotonate and cyclopent-2-enone, respectively, were also obtained as *anti/syn* diastereomers.[4,17] In the last case no 1,2-addition reaction to the carbonyl was observed.



Scheme 1.

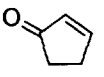
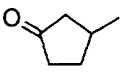
Representative compounds **7** have been reductively desulphonylated with sodium amalgam in methanol buffered by Na_2HPO_4[18] at -20°C to lead to the stereoselective preparation of compounds **9**. In the case of benzyl bromide the mixture of **7b** and **8b** and diastereomeric compounds **7f** and **7h** were reduced to compounds **9b**, **9f** and **9h**, respectively. The reductive deconjugation of compounds **7** is due to the formation of the corresponding dienolates under the basic reduction conditions, which suffered kinetic protonation at the α-position of the amide.



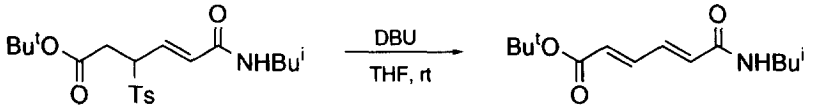
9b (96 %) **9f** (75%) **9h** (98%)

Basic elimination of compound **7c**, derived from *tert*-butyl bromoacetate, with DBU at room temperature overnight gave stereoselectively the corresponding (2*E*,4*E*)-diene-1,6-dicarboxylate derivative **10c** in 96% yield (Scheme 2).

Table 1. Reaction of Dianion **6** with Electrophiles. Preparation of Compounds **7**.

		product[a]			
entry	electrophile	no.	X	yield (%)[b]	mp (°C)[c] or R_f[d]
1	CH_3OD	**7a**	D	82	164-165
2	$PhCH_2Br$	**7b**	$PhCH_2$	55[e]	0.82
3	$Bu^tO_2CCH_2Br$	**7c**	$Bu^tO_2CCH_2$	72	64-65
4	Pr^iCHO	**7d**	Pr^iCHOH	53[f]	0.61, 0.71
5	Bu^tCHO	**7e**	Bu^tCHOH	57[g]	0.66
6	$n\text{-}C_5H_{11}CHO$	**7f**	$n\text{-}C_5H_{11}CHOH$	66[h]	0.56
7	$PhCH_2CHO$	**7g**	$PhCH_2CHOH$	43[h]	0.62
8	(*E*)-$MeCHCHCO_2Me$	**7h**	$MeCHCH_2CO_2Me$	66[i]	0.60
9		**7i**		71[j]	0.30

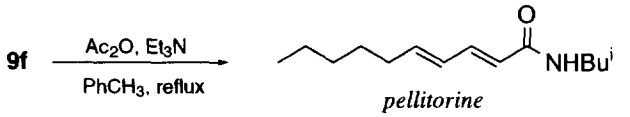
[a] All products were pure (TLC, 300 MHz ^1H NMR) and gave satisfactory spectral data (IR, ^1H and ^{13}C NMR, and mass spectra). [b] Isolated yield after column chromatography on silica gel, based on amide **5b**. Diastereomeric ratios were determined by NMR. [c] Hexane/EtOAc. [d] Hexane/EtOAc: 1/4. [e] Compound **8b** (Scheme 1) was also obtained in 13% yield. [f] 4/1 Mixture of *erythro/threo* diastereomers. [g] Only the *erythro* diastereomer was obtained. [h] 3/1 Mixture of *erythro/threo* diastereomers. [i] 2/1 Mixture of *anti/syn* diastereomers. [j] 1.5/1 Mixture of *anti/syn* diastereomers.



7c **10c**

Scheme 2.

Isobutylamine was chosen as amine to prepare the starting amide **5b** in order to transform hydroxyamide **9f** stereoselectively into the natural dienamide pellitorine[19] by treatment with acetic anhydride and triethylamine under toluene reflux for 3 d in 70% yield (Scheme 3). Direct transformation of hydroxy sulfone **7f** into pellitorine was partially achieved by SmI_2 induced reduction in THF at -20°C.[21] In this case pellitorine and hydroxyamide **9f** were obtained after column chromatography in 32 and 30% yield, respectively.



pellitorine

Scheme 3.

In summary, we have demonstrated that dilithiated (*E*)-*N*-isobutyl-4-tosyl-2-butenamide, readly accessible from vinylacetic acid, is a good intermediate for the regiospecific and stereoselective γ-functionalization of crotonamide. Moreover, the presence of the sulfone group at the γ-position allowed the stereoselective synthesis of β,γ-unsaturated δ-hydroxyamides and also of (2*E*,4*E*)-dienamides,[22] such as pellitorine.

Acknowledgments. We are very grateful to the DGICYT, Spain (Project no. PB94-1515) for financial support and to Almu S.A. for a generous gift of TBTU. F. C. thanks ASAC Pharmaceutical International for a grant.

REFERENCES AND NOTES

1. (a) Cainelli, G.; Cardillo, G.; Contento, M.; Trapani, G.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 400-404. (b) Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, 4249-4252. (c) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433-2436. (d) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925-4935. (e) Katzenellenbogen, J. A.; Savu, P. M. *J. Org. Chem.* **1981**, *46*, 239-250. (f) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163-167. (g) Galatsis, P.; Millan, S. D.; Nechala, P.; Ferguson, G. *J. Org. Chem.* **1994**, *59*, 6643-6651.
2. (a) Casinos, I.; Mestres, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1651-1655. (b) Johnson, P. R.; White, J. D. *J. Org. Chem.* **1984**, *49*, 4424-4429. (c) Ballester, P.; Costa, A.; García-Raso, A.; Mestres, R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 21-32. (d) Ballester, P.; Costa, A.; García-Raso, A.; Mestres, R. *Tetrahedron Lett.* **1987**, *28*, 3853-3856. (e) Parra, M.; Mestres, R.; Aparicio, D.; Durana, N.; Rubiales, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 327-332.
3. Deshmukh, A. R.; Trau, L.; Biehl, E. R. *J. Org. Chem.* **1992**, *57*, 667-670.
4. Haynes, R. K.; Starling, S. M.; Vonwiller, S. C. *J. Org. Chem.* **1995**, *60*, 4690-4691.
5. (a) Lansbury, P. T.; Erwin, R. W. *Tetrahedron Lett.* **1978**, 2675-2678. (b) Lansbury, P. T.; Erwin, R. W; Jeffrey, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1602-1608. (c) See note 27 in previous reference 5b.
6. Kende, A.S.; Constantinides, D.; Lee, S. J.; Liebeskind, L. *Tetrahedron Lett.* **1975**, 405-408.
7. Purchased from Aldrich.
8. This methodology is a simple and easy way for preparing vinyl sulfones[9] and avoids the use of chlorinated solvents and the preparation of the very unstable tosyl iodide.[10]
9. (a) Nájera, C.; Sansano, J. M.; Yus, M. *J. Chem. Educ.* **1995**, *72*, 664-665. (b) Caturla, F.; Nájera, C. *Tetrahedron Lett.* **1996**, *37*, in the press.
10. da Siva Corrêa, C. M. M.; Fleming, M. D. C. M.; Oliveira, M. A. B. C. S.; Garrido, E. M. J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1993-2000.
11. The iodosulfonylation of 3-butenenitrile with tosyl iodide in carbon tetrachloride followed by dehydroiodination with triethylamine in benzene is not a stereoselective process affording a *ca.* 1/1 mixture of *Z*/*E*-4-tosyl-2-butenenitrile.[10]
12. The dilithiation of acid **5a** and reaction with electrophiles gave lower yields.
13. Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927-1930.
14. The structure of this dianion could be represented by as *exo* and/or *s-trans* conformations as has been proposed for the dienolate of 2-butenoic acid: (a) Aurell, M. J.; Gil, S.; Mestres, R.; Parra, M.; Tortajada, A. *Tetrahedron* **1994**, *50*, 5109-5118. (b) Domingo, L. R.; Gil, S.; Mestres, R.; Picher, M. T. *Tetrahedron* **1995**, *51*, 7207-7214.
15. Configurational assignments were made according to coupling constants values for vicinal protons in β-hydroxy sulfones:[16] J_{threo} = 8-10 Hz and $J_{erythro}$ = 1-2.5 Hz.
16. Truce, W. E.; Klinger, T. C. *J. Org. Chem.* **1970**, *35*, 1834-1838.
17. Configurational assignement could not be carried out according to ref. 4, due to the overlapping of olefinic signals.
18. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477-3478.
19. Pellitorine has been found in a number of *Piper* species as well as in the Compositae and Rutaceae families and has antitubercular and potent insecticidal activity[20] (e. g. paralyzing effect on houseflies). For recent synthesis see: (a) Kaga, H.; Ahmed, Z.; Gotoh, K.; Orito, K. *Synlett* **1994**, 607-608. (b) Plobeck, N. A.; Bäckvall, J.-E. *J. Org. Chem.* **1991**, *56*, 4508-4512.
20. Likhitwitayawuid, K.; Ruangrungsi, N.; Lange, G. L.; Deacco, C. P. *Tetrahedron* **1987**, *43*, 3689-3694 and references cited therein.
21. Künzer, H.; Stankhe, M.; Sauer, G.; Weichert, R. *Tetrahedron Lett.* **1991**, *32*, 1949-1952.
22. For other stereoselective synthesis of (2*E*,4*E*)-dienamides see: Bernabeu, M. C.; Chinchilla, R.; Nájera, C. *Tetrahedron Lett.* **1995**, *36*, 3901-3904 and references cited therein.

(*Received in UK* 11 *April* 1996; *revised* 13 *May* 1996; *accepted* 17 *May* 1996)