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Diastereoselective alkylations of β-tetrazolyl propionic acids

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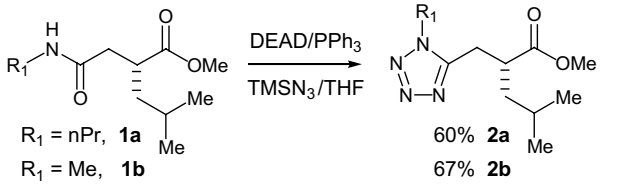
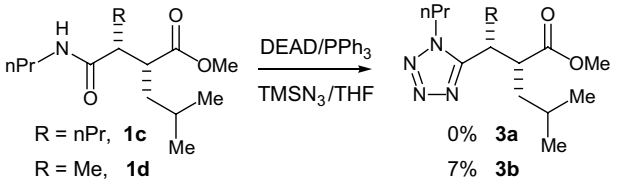
Abstract—A new procedure for the diastereoselective alkylations of β-tetrazolyl propionic acids is described. A seven-membered chelation model is proposed to rationalize the observed high level of *syn* selectivity.

Emerging evidence suggests that a tetrazole moiety can function as a metabolically stable bioisostere of a carboxylate or an amide.[1] Since tetrazole rings are structural motifs in many medicinal compounds, new methodologies capable of making novel tetrazole derivatives are useful.[2] Recently, we wanted to prepare tetrazole analogs **2** and **3** for our research. Although the synthesis of tetrazole **2** from **1** was straightforward (Eq. 1),[3] the preparation of β-substituted tetrazole **3** was problematic (Eq. 2).[4] It is evident from the data that the size of R group within **1** has an influence on the yield of the tetrazole formation. We presumed the poor yield was due to the steric hindrance of the substrates.

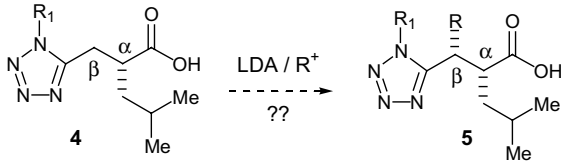
In this letter, we wish to describe an LDA-promoted alkylation protocol to access the β-substituted tetrazoles illustrated in Eq. 3. Although a simple α-tetrazole methylation reaction has been documented,[5] the generality of such reaction and the related diastereoselective process have not been studied. The products derived from the reactions illustrated in Eq. 3 are bioisosteres of succinates that have been used extensively in the preparation of MMP inhibitors.[6]



(1)



(2)



(3)

Table 1 summarizes the electrophile, diastereoselectivity, and yield for each reaction studied.[7] The addition of allylbromide to **4** generated from 2.5 equiv of LDA[8] resulted in a diastereomeric ratio 30:1 favoring the *syn* adduct **5a** in 92% yield (entry 1).[9] The high level of *syn* selectivity was also observed in a related succinate synthesis, which may be explained by invoking the cyclic transition state illustrated in Eq. 4.[10] We speculate that the electrophile R^+ approaches the nucleophile from the opposite side of the bulky isobutyl group in the cyclic intermediate leading to the *syn* isomer **5a**. The structure of *syn* isomer **5a** was unequivocally established by X-ray crystallography.

Keywords: tetrazole; diastereoselectivity; alkylation; chelation biol.
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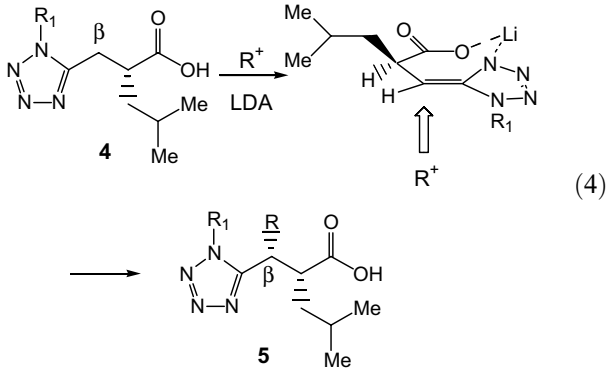
Table 1. Alkylations of substrate **4**

Entry	R_1	R^+	*syn*:*anti*[a]	Adduct (yield, %)
1	*n*Pr	allylBr	30:1	**5a** (92)[b]
2	*n*Pr	MeI	11:1	**5b** (95)[b]
3	*n*Pr	BnBr	30:1	**5c** (67)[c]
4	*n*Pr	*i*PrBr	30:1	**5d** (45)[c]
5	*n*Pr	Tris–N_3	25:1	**5e** (52)[c]
6	Me	BnBr	15:1	**5f** (45)[c]
7	Me	allylBr	20:1	**5g** (40)[c]
8	Me	*i*PrBr	20:1	**5h** (42)[c]
9	*n*Pr	EtBr	30:1	**5i** (58)[c]

[a] Ratios determined by HPLC analysis on the crude products.
[b] Crude yield.
[c] Isolated yield after HPLC purification.



In the illustrated examples, the stereochemical outcome was uniformly high, favoring the *syn* isomer (Table 1).[11] The chemical yield was excellent for entries 1–2, but only moderate for entries 4–9.[12] The current methodology has been shown to work with both sterically demanding electrophile (entries 4 and 8) and trisyl azide (entry 5). The azide group was subsequently reduced to an amine and served as a β-amino acid synthon. Within this limited set of analogs, changing the substituents on the tetrazole ring showed a minimal effect on the reaction diastereoselectivity. Currently, the scope and limitations of related reactions are being investigated.

References and Notes

1. (a) Singh, H.; Chawla, A.; Kapoor, V.; Paul, D.; Malkorta, R. *Progr. Med. Chem.* **1980**, *17*, 151; (b) Prous, J. R., Ed. *Drugs Future* **1990**, *15*, 549; (c) Duncia, J. V.; Santella, J. B.; Higley, A.; VanAtten, M. K.; Weber, P. C.; Alexander, R. S.; Kettner, C. A.; Pruitt, J. R.; Liauw, A. Y.; Quan, M. L.; Knabb, R. M.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 775.
2. (a) Wong, P. C.; Price, W. A., Jr:, Chiu, A. T.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. *Hypertension* **1990**, *15*, 459; (b) Gapinski, D. M.; Roman, C. R.; Rinkema, L. E.; Fleisch, J. H. *J. Med. Chem.* **1988**, *31*, 172; (c) Bernstein, P. R.; Vacek, E. P. *Synthesis* **1987**, 1133; (d) Thomas, E. W.; Cudahy, M. M. *J. Org. Chem.* **1993**, *58*, 1623.
3. Tetrazole formation conditions: Duncia, J. V.; Pierce, M. E.; Santella, J. B., III. *J. Org. Chem.* **1991**, *56*, 2395, The starting material, 2-isobutyl succinic acid 1-methyl ester, was purchased from Lancaster.
4. Other related reaction conditions were also examined. However, the results were less than satisfactory, see: Thomas, E. W. *Synthesis* **1993**, 767.
5. Thomas, E. W.; Cudahy, M. M. *J. Org. Med. Chem.* **1993**, *58*, 1623.
6. Robinson, R.; Ragan, J.; Cronin, B.; Donahue, K.; Mitchell, P.; Reeves, L.; Yocum, S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1719.
7. Representative experimental procedure: To a solution of acid **4a** (entry 1; 100 mg, 0.42 mmol) in THF (5 mL) at −78 °C was added LDA (0.52 mL, 1.04 mmol), followed by allylbromide (0.04 mL, 0.5 mmol) 30 min later. The reaction was stirred from −78 °C to rt for 20 h, quenched with H_2O, and then diluted with Et_2O. The aqueous layer was collected, acidified to pH = 3 with 1 N HCl, and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give clean product **5a** in 92% yield.
8. It is worth mentioning that both LiHMDS and NaHMDS were also examined as potential bases to enolizing acid **4**. However, in both cases, the reactions failed to provide any desired products and only gave the starting material.
9. Although the minor *anti*-diastereoisomer was not sufficient to be isolated, its existence was confirmed by LC/MS spectrometer. Given the result of excellent diastereoselectivity, we decided not to change the solvent or to add any chelate additives to affect the reaction diastereoselectivity.
10. For related seven-membered ring transition states involving succinate enolates see: (a) Beckett, R. P.; Crimmin, M. J.; Davis, M. H.; Spavold, Z. *Synlett* **1993**, 137; (b) Flippin, L. A. *Tetrahedron Lett.* **1991**, *32*, 6857.
11. The bias for the *syn* selection was further confirmed by comparison of the ^1H NMR spectra of compound **5b** and the saponification product **3b**. Compound **3b** was synthesized from intermediate **1d** as illustrated in Eq. 2. For both stereocenters in **1d**, the absolute stereoconfiguration is known.
12. For entries 4–9, some of the unreacted starting materials were recovered during the purification process.