ORGANIC LETTERS

2005
Vol. 7, No. 4
561−564

Efficient Syntheses of 5-Aminoalkyl-1*H*-tetrazoles and of Polyamines Incorporating Tetrazole Rings

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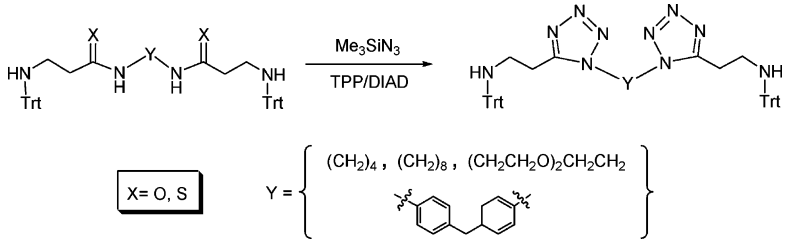
Received November 8, 2004

ABSTRACT



Linear N^{ω}-tritylated ω-amino thiobenzylamides and N^{α},N^{ω}-ditritylated polyamino mono- or bisthioamides were efficiently converted to the corresponding tetrazole derivatives upon treatment with azidotrimethylsilane under Mitsunobu reaction conditions.

5-Substituted 1*H*-tetrazoles and 1,5-disubstituted tetrazoles are often used as metabolism-resistant isosteric replacements for carboxylic acids and as *cis* amide bond surrogates, respectively, in SAR-driven analogue synthesis in medicinal chemistry.[1−3] A variety of synthetic tetrazole-containing biologically active substances are described in the current literature, such as glycine−tetrazole modified *S*-alkyl-GSH analogues,[4] α-methylene tetrazole-based peptidomimetic HIV protease inhibitors,[5] endothelin-converting enzyme-1 (ECE-1),[6] neutral endopeptidase 24.11 (NEP 24.11) non-peptidic inhibitors,[7] and urea-based inhibitors of glutamate carboxypeptidase II (GCPII).[8] 5-Substituted 1*H*-tetrazoles are usually prepared by the reaction of nitriles or secondary amides under Mitsunobu reaction conditions with azides, especially with tributyltin or trimethylsilyl azide which are safer and soluble in organic solvents.[1,9,10] On the other hand, 1,5-disubstituted tetrazoles have been obtained through sequential treatment of secondary amides with PCl_5 and HN_3.[2] We have developed a general methodology for the synthesis of polyamines based on the acylation of suitable amines by either the isolable succinimidyl ester of *N*-trityl-β-alanine (Trt-βAla-OSu, **1**)[11] or the in situ activated *N*-trityl-γ-aminobutyric acid (Trt-γAba, **3**)[12] with *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt), followed by $LiAlH_4$-mediated reduction of the resulting

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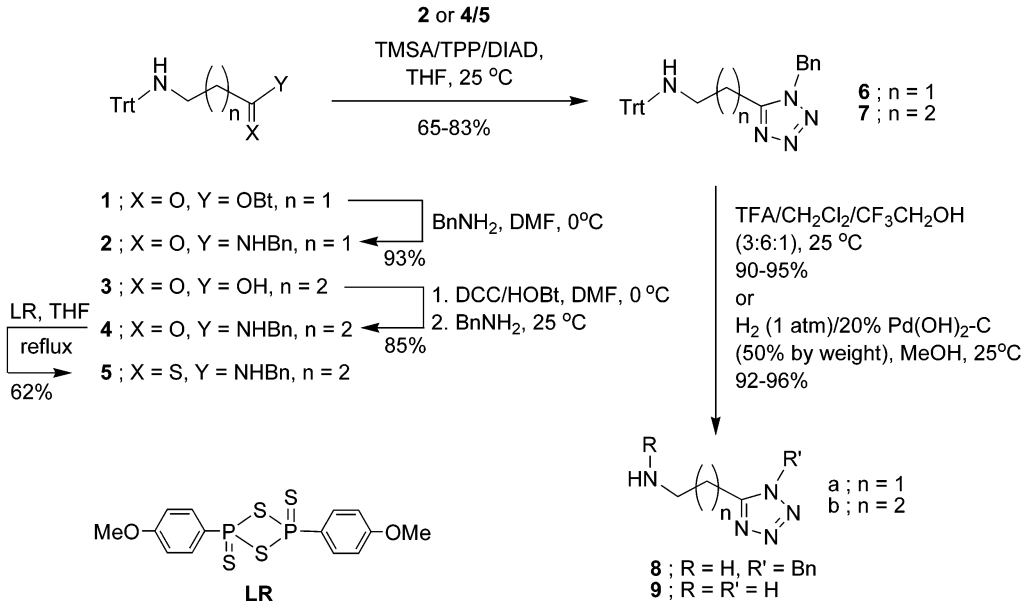
10.1021/ol0477069 CCC: $30.25
Published on Web 01/27/2005

Scheme 1. Conversion of N^{ω}-Tritylated Linear ω-Amino Benzylamides to Tetrazole Derivatives



mono- or polyamides.[12] We therefore thought it would be of interest to examine the suitability of these mono- or polyamides to prepare for the first time polyamine analogues incorporating one or more tetrazole rings.

We initially examined the suitability of the benzylamides Trt-βAla-NHBn (**2**) and Trt-γAba-NHBn (**4**),[12] taken as model compounds to react with either commercially available tributyltin azide (TBTA) or trimethylsilyl azide (TMSA), in the presence of triphenylphosphine (TPP) and diisopropyl azodicarboxylate (DIAD). These benzylamides were readily obtained through the acylation of benzylamine with **1** and **3**, respectively, in 93% and 85% yields (Scheme 1). It was found that both benzylamides **2** and **4** reacted at a similar rate (e.g., reaction completed within 3 days at 25 °C) with TMSA in the presence of TPP and DIAD and produced similar yields (see Table 1) of the anticipated tetrazole derivatives **6** and **7**, respectively, using 2.4−2.9 equiv of reagents. For comparison, the more sterically demanding reagent TBTA produced a less than 10% yield of tetrazole **6** after 7 days at the same temperature. At this point, we reasoned that the corresponding thioamides would react faster and more efficiently under these reaction conditions.[13] Thus, treatment of benzylamide **4** with Lawesson's reagent (LR) produced a 62% yield of the corresponding thioamide **5**. This was then treated with the combination of reagents TMSA/TPP/DIAD to give an 83% yield of the tetrazole **7** within 1 h, without the need to add excess reagents. From the resulting fully protected tetrazoles **6** and **7**, the Trt group can be selectively removed by trifluoroacetic acid (TFA)-mediated acidolysis (TFA−CH_2Cl_2−CF_3CH_2OH = 3:6:1) to give the partially protected 5-(ω-aminoalkyl)tetrazoles **8**, whereas both protecting groups can be removed in one pot by catalytic hydrogenolysis (the Trt group is cleaved much faster than

Table 1. Thionation of Secondary Amides with LR and Conversion of Amides and Thioamides to Tetrazoles Using TMSA, TPP, and DIAD[a]

entry	starting material	reaction time (h)	product	yield (%)
1	**2**	36	**6**	65
2	**4**	0.5[b]	**5**	62
3	**4**	36	**7**	68
4	**5**	1	**7**	83
5	**14**	2	**16**	50
6	**16**	24	**17**	50
7	**19**	12	**20**	85
8	**19**	72	**21**	33
9	**20**	24	**21**	90
10	**22**	2[b]	**23**	50
11	**23**	24	**28**	55
12	**24**	2	**25**	55
13	**25**	16	**29**	55
14	**26**	12	**27**	51
15	**27**	6	**32**	50
16	**34**	12[b]	**36**	75
17	**34**	3[b]	**35**	25
18	**35**	5	**36**	52

[a] The structures of new compounds described in this paper were determined by a combination of spectroscopic techniques (ESI-MS, NMR) and microanalysis. Fully deprotected mono- or bistetrazole polyamine derivatives were characterized by MALDI-TOF/TOF HR-MS. [b] THF, reflux. All other reactions presented in the table were perfomed at ambient temperature.

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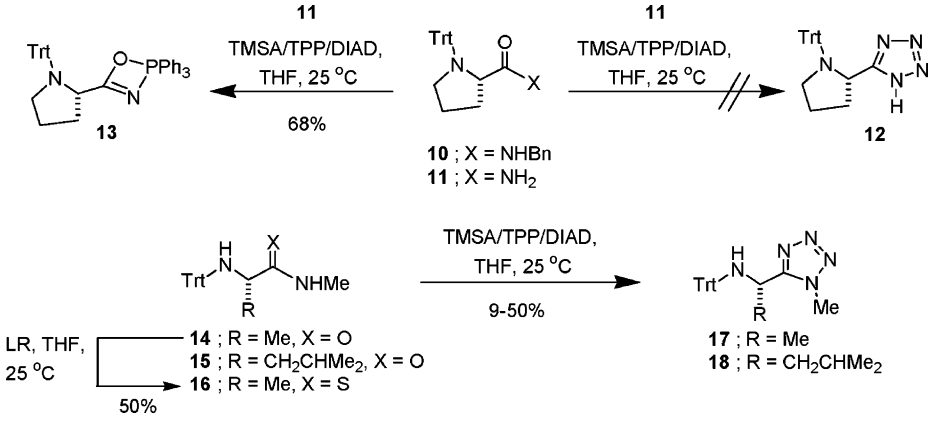
Scheme 2. Attempted Conversion of N^{α}-Tritylated Chiral α-Amino Benzylamides to Tetrazole Derivatives



the Bn group) within 16−20 h to give the free 5-(ω-aminoalkyl)tetrazoles **9** in 92−96% yield.

Attempts to extend this reaction to benzylamides of N^{α}-tritylated L-amino acids, like Pro (**10**), Phe, Leu, Val, and Ala, readily obtained through a reported procedure,[14] were unsuccessful, as were attempts to convert these benzylamides to the corresponding thioamides using the reagent LR. It is worth mentioning that treatment of amide **11** with TMSA/TPP/DIAD, to obtain tetrazole **12**, led instead to compound **13** in 68% yield, following flash column chromatography (FCC) purification. Compound **13** was also obtained from the reaction of **11** with TPP and DIAD (Scheme 2). It should be noted that **13** was stable even at refluxing THF or toluene for several hours.

It was suspected that steric hindrance was the cause for these failed conversions of N^{α}-tritylated α-amino benzylamides to tetrazoles, and therefore, the corresponding methylamides were employed. Only the methylamides **14** and **15** from Ala and Leu, respectively, reacted however sluggishly with TMSA/TPP/DIAD to provide the corresponding tetrazoles **17** and **18** in low yields (ca. 10%).[15] Attempted thionation of **15** gave a complex reaction mixture whereas the less sterically demanding methylamide **14** provided the expected thioamide **16** in 50% yield following FCC purification. From this thioamide, the tetrazole **17** was now obtained in 50% yield.

We then turned our attention to the application of this methodology to the monoamide **19**[16] and the bisamide **22** (Scheme 3).[12,17] Treatment of **19** with a total of 4.5 equiv of each of TPP, DIAD, and TMSA within 3 days at 25 °C gave a 33% yield of the tetrazole derivative **21**, whereas bisamide **22** failed to produce the expected bistetrazole derivative **28**, obviously due to the low solubility of **22** in the reaction medium (anhydrous THF or dioxane). However, even in DMF, in which **22** was solubilized upon addition of the reagents, only a less than 10% (as judged by TLC) conversion to **28** was observed after repeated additions of reagents and several days at 25 °C. On the other hand, treatment of either **19** or **22** with LR in THF for 12 h at 25 °C, or 2 h under reflux, respectively, produced the corresponding mono- (**20**) and bis-thioamides (**23**) in 85% and 50% isolated yields, respectively. From these thioamides the corresponding mono- (**21**) and bis-tetrazole (**28**) derivatives were unexceptionally obtained in 90% and 55% yields, respectively. It is worth mentioning that transformation of **23** to its corresponding mono-tetrazole derivative was over within 1 h, whereas its complete conversion to the bistetrazole derivative **28** required additional reagents and a much longer reaction time.

Similarly, the bisamides **24** and **26**[17] were converted first to the corresponding bisthioamides **25** and **27** in 55% and 51% yields, respectively, and then reacted with TMSA in the presence of TPP and DIAD to give the bistetrazole derivatives **29** and **32** in 55% and 50% yields, respectively. Routine detritylation of these tetrazole derivatives gave unexceptionally the polyamines **30**, **31,** and **33** in 90−95% yields, incorporating one or two tetrazole units. The former may be considered as an analogue of spermidine (SPD) whereas the other two are analogues of spermine (SPM).

This methodology was easily extended to accommodate aromatic polyamines, like the one obtained by the $LiAlH_4$-mediated reduction of the bisamide **34**.[18] Tetrazole ring formation was effected in refluxing THF for 12 h to give the expected bistetrazole derivative **36** in 75% yield. On the other hand, thionation of **34** gave the corresponding bisthioamide **35** in low yield (25%). However, this compound was converted to **36** in 52% yield at ambient temperature.

In conclusion, the present methodology provides easy access to linear 5-aminoalkyl-1*H*-tetrazoles and polyamines incorporating tetrazole units in their skeleton, by activating,

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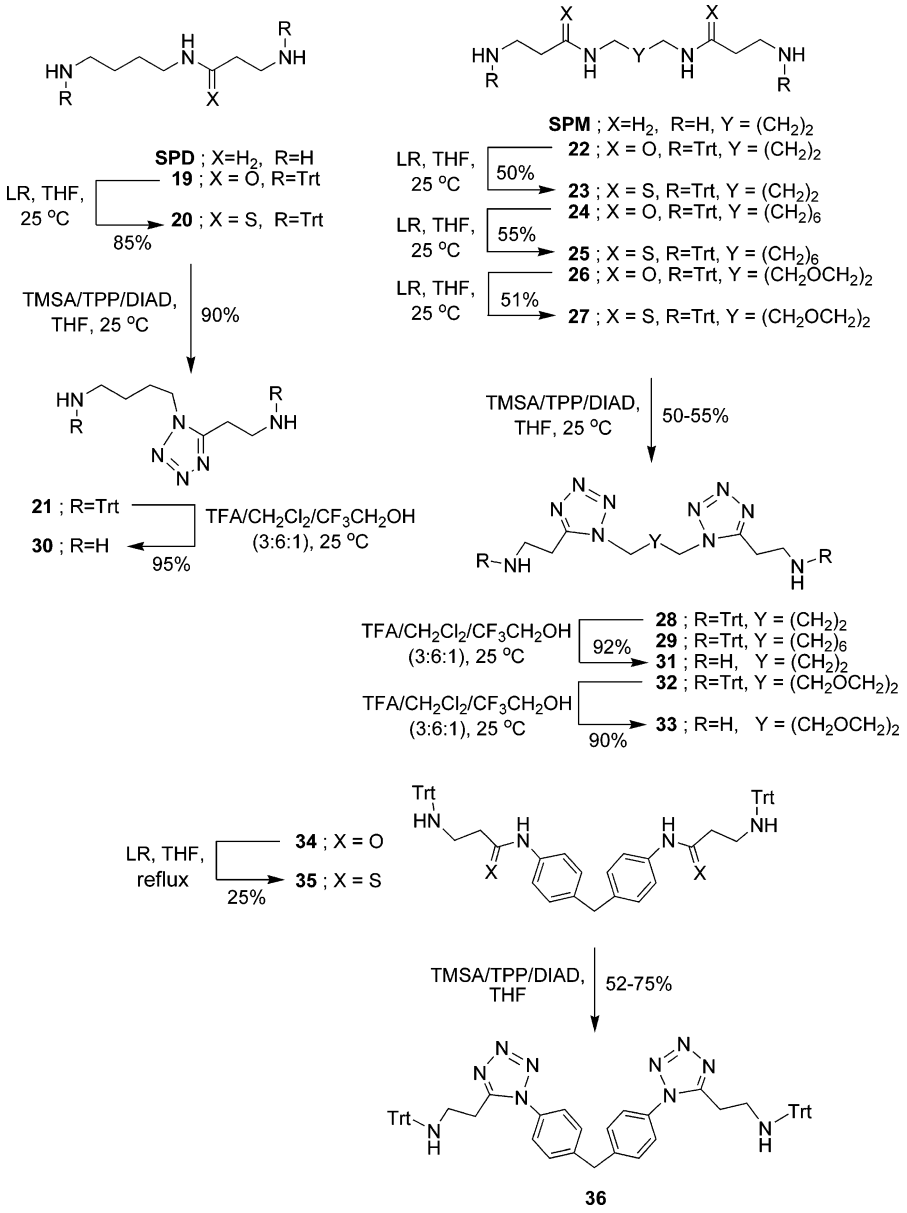
Scheme 3. Synthesis of Polyamines Incorporating Tetrazole Rings



where necessary, secondary amide bonds through thionation toward their reaction with azidotrimethylsilane under Mitsunobu reaction conditions. Further applications of this methodology, as well as tests to determine the biological activity of these novel, fully deprotected, polyamine analogues, are currently in progress.

Acknowledgment. Prof. Giovanni Sindona and Dr. Anna Napoli from the Department of Chemistry of the University of Calabria (Italy) are gratefully acknowledged for providing the HR-MS analysis.

Supporting Information Available: General synthetic procedures and spectroscopic data for compounds **6** and **13** and for selected tritylated polyamine analogues incorporating tetrazole ring(s). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0477069