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PREPARATION OF 5-TETRAZOLYL GROUPS FROM CARBOXYLIC ACIDS. A SEQUENCE AMENABLE TO SENSITIVE SUBSTRATES

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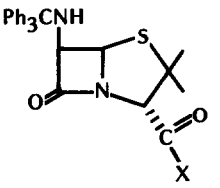
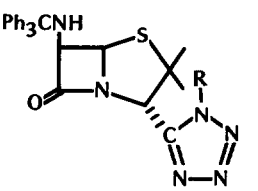
The 5-tetrazolyl group is a frequently studied and therapeutically useful bioisostere of the carboxylic acid group[1-3]. The preparation of 5-monosubstituted tetrazoles generally employs procedures starting with the carboxylic acid moiety[2,3], but these are not always applicable to sensitive molecules. The most commonly employed reaction (azide addition to a nitrile) generally requires forcing conditions. While mild procedures are known for the preparation of 5,N-disubstituted tetrazoles, conditions[2,3] for removing the N-substituent may then be incompatible with other functionalities existing in the substrate.

We now report an alternative procedure for carboxyl-to-5-tetrazole conversion, the key feature of which is a mild deblocking reaction of certain readily prepared 1,5-disubstituted tetrazoles. Specifically, we demonstrate the application of our approach to the synthesis of a 3-(5-tetrazolyl)penam, in which the C-3 carboxyl of N-trityl-6-amino-penicillanic acid is transformed to the corresponding 5-tetrazolyl group. The 3-(5-tetrazolyl)penam group has been synthesized by other attractive and efficient routes[4]; it is chosen as the illustrative example for this communication to show the applicability of our $RCO_2H \rightarrow RCN_4H$ synthesis procedure to a sensitive molecule. The novel microbiological properties of CP-35,587 (compound 6), one of the 3-(5-tetrazolyl)-penam derivatives, have been described[5].

Reported observations[6-8] showed that N-propionate derivatives of tetrazoles could undergo retro-Michael eliminations to give tetrazoles unsubstituted on nitrogen. However, forcing conditions (refluxing hydroxide) that are incompatible with sensitive functionality such as a β-lactam were used. The synthetic utility of this transformation has not been exploited (because the observed eliminations occurred as undesired side reactions). It appeared to us that if mild conditions could be found to effect the retro-Michael deblocking, a useful procedure for the $RCO_2H \rightarrow RCN_4H$ transformation would be available for sensitive molecules.



1 X = –OH
2 X = –NHCH$_2$CH$_2$CO$_2$CH$_3$



3 R = –CH$_2$CH$_2$CO$_2$CH$_3$
4 R = –H

Tritylaminopenicillanic acid (1)[9] was converted to amide 2 by application of the procedure of Brown[10] for preparation of penicillin 3-carboxamides. Activation of 1 (in $CHCl_3$, Et_3N) with EtOCOCl followed by $H_2NCH_2CH_2CO_2CH_3$[11] afforded amide 2 (98%) mp 60-70°; ir (KBr) 5.63, 5.76 and 6.00μ; ms 300.1022 (M^+–Ph_3C). Conversion of amide 2 to an iminochloride intermediate[2,3] with phosgene ($CHCl_3$, pyridine, RT/2.5 hrs) and addition of tetramethylguanadinium azide (or trimethylsilyl azide) followed by overnight contact at ambient temperature afforded the 1,5-disubstituted tetrazole 3 in high yield and good purity. Recrystallization from methanol gave 3 (48%) mp 102-105°; $C_{31}H_{32}N_6SO_3$; ir (KBr) 5.66, 5.80 6.96μ; nmr ($CDCl_3$) δ 1.17 (s, 3H), 1.70 (s, 3H), 3.10 (t, 2H), 3.70 (s, 3H), 3.80 (m, 5H), 5.15 (s, 1H), 7.40 (m, 15H); ms 326.1114 (M^+–Ph_3C).

The selective deblocking of 3 to the desired 5-tetrazole product 4 was realized by use of the amidine DBN (1,5-diazabicyclo[4.3.0]non-5-ene) in $CHCl_3$. According to nmr observations of reaction mixtures, this deblocking occurred cleanly and within minutes at room temperature. One equivalent of DBN was sufficient for obtaining a 65% isolated yield of 4. Use of three equivalents of DBN led to a 71% isolated yield of 5-monosubstituted penicillin tetrazole 4, mp 114°; $C_{27}H_{26}N_6SO$; ir (KBr) 5.59μ; nmr (DMSO-d_6) δ 0.78 (s, 3H), 1.58 (s, 3H), 3.35 (d, 1H), 4.60 (m, 2H), 5.30 (s, 1H), 7.40 (m, 15H), 8.28 (s, 1H). Separate studies showed that the excess DBN did not have detrimental effects even when the deblocking reaction was allowed to proceed several hours. Losses presumably occurred during workup (wash $CHCl_3$ with 2N HCl, cool and filter off precipitate), which has not been optimized.

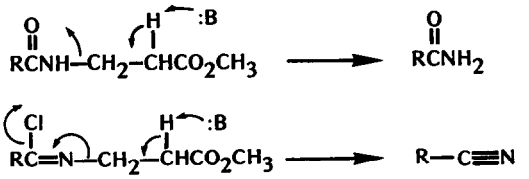
An interesting aspect of the DBN deblocking procedure is that methyl acrylate, an expected side product, is not observed in the nmr spectra of reaction mixtures. It undergoes a Michael addition with DBN to give a quaternary adduct. This fortuitous post-deblocking reaction served to minimize potential workup complications in other systems (where the product did not crystallize from the reaction solvent) because the side products could be readily washed from acidified solutions of the tetrazole. The protonated tetrazoles remainded in the organic layer.

The deblocking procedure also occured rapidly at room temperature with other bases such as K_2CO_3, KOtBu, LiOMe, NaOMe and acetamidine. However, in these cases the β-lactam functionality was destroyed. Nevertheless, these procedures were synthetically useful for

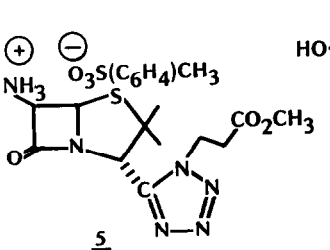
separately-studied substrates that did not contain a β-lactam. Use of Et_3N, pyridine, or their hydrochlorides at room temperature were insufficient conditions for deblocking. Addition of 1/10 equivalent DBN to the latter systems allowed deblocking only to the extent of added DBN.

Groups other than methyl proprionate also serve for the retro-Michael approach to 5-tetrazoles. For example, we have used $H_2NCH_2CH_2SO_2Ph$ successfully (in addition to $H_2NCH_2CH_2CO_2CH_3$) for other $RCO_2H \rightarrow R(CN_4H)$ syntheses by our sequence. Deblocking of the sulfone was also accompanied by Michael addition of the base to the liberated phenyl vinyl sulfone. Besides DBN, acetamidine, K_2CO_3 and alkoxides served well in the deblocking step for substrates that did not contain the β-lactam functionality. As an aside, it is worth mentioning that yields for the various steps in other systems were generally very good.

The scope of the total $RCO_2H \rightarrow RCN_4H$ reaction sequence with blocking/deblocking groups containing deblocking-activating groups stronger than carbomethoxy or sulfone (so that weaker bases could be used in the deblocking) has not been explored; premature deblocking might be a problem. Undesired deblocking of the type indicated below did not occur with the Et_3N or pyridine present in the reaction sequence to prepare the ester- or sulfone-containing 1,5-disubstituted tetrazoles. The relevant amides and nitriles were available for comparison purposes. They were not detected by TLC of reaction mixtures.



The propionate ester group appeared relatively stable to acidic condition, which might occur in synthetic sequences where the disubstituted tetrazole experiences other reaction conditions before the RCN_4H is liberated. Thus, the trityl group (which served in our sequence as a protecting group for the 6-amino function as well as providing solubility in the reaction solvent) was readily removed from intermediate 3 by employing the procedure of Koe[12] which



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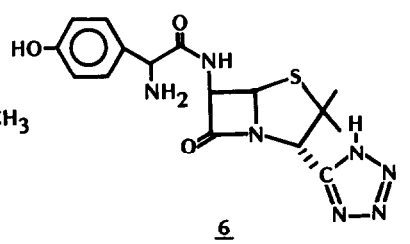

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involves dissolving 3 in acetone and adding one equivalent of p-toluenesulfonic acid monohydrate (1 hr/R.T.) to afford as a precipitate the crystalline salt 5, (69%) mp 157-160°; ir (KBr) 5.54, 5.76μ; nmr (DMSO-d_6) δ 1.12 (s, 3H), 1.70 (s, 3H), 2.24 (s, 3H), 3.00 (t, 2H), 3.55 (s, 3H), 4.59 (5, 2H), 4.86 (d, 1H) 5.52 (s, 1H), 5.64 (d, 1H) 7.00 (d, 2H), 7.53 (d, 2H)

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