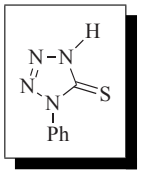
1-Phenyl-2-tetrazoline-5-thione



[86-93-1] $C_7H_6N_4S$ (MW 178.24)
InChI = 1S/C7H6N4S/c12-7-8-9-10-11(7)6-4-2-1-3-5-6/h1-5H,(H,8,10,12)
InChIKey = GGZHVNZHFYCSEV-UHFFFAOYSA-N
(Na salt)
[15052-19-4]
InChI = 1S/C7H6N4S.Na/c12-7-8-9-10-11(7)6-4-2-1-3-5-6;/h1-5H,(H,8,10,12);/q;+1/p-1
InChIKey = RSZMKAPXKXEWBY-UHFFFAOYSA-M

(in combination with isocyanides, activates carboxylate for lactonization,[1] peptide formation;[2] source of nucleophilic sulfur[3])

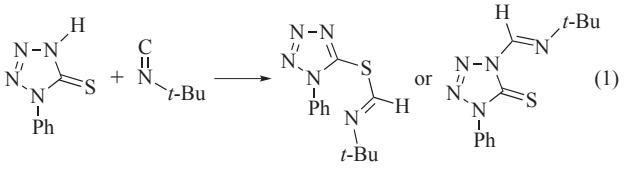
Physical Data: mp 150 °C (dec).
Solubility: sol organic solvents.
Form Supplied in: red solid; widely available.
Handling, Storage, and Precautions: store in dark.

Original Commentary

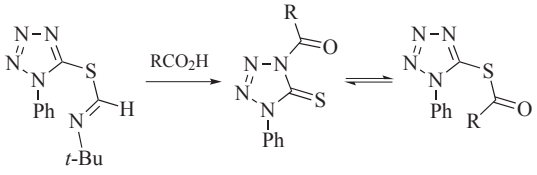
Richard T. Taylor
Miami University, Oxford, OH, USA

Introduction. While this reagent has a wide variety of applications of great value to the photographic industry, it is also a synthetic reagent of some utility. These applications relate to activation of the carboxylate group, introduction of nucleophilic sulfur, and as a heterocyclic building block.

Reaction with Isocyanides. Treatment of the reagent with ***tert-Butyl Isocyanide*** affords an intermediate of the nature indicated (eq 1). Subsequent reaction with a carboxylic acid at −40 °C gives an equilibrium mixture of compounds (eq 2) in which the carbonyl group is activated toward nucleophilic substitution. This intermediate can be effectively utilized in two ways.



(1)



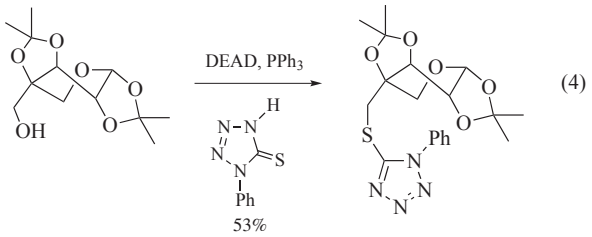
(2)

Lactone Formation. Long-chain hydroxy acids can, by this method, be converted into lactones (eq 3).[1] Of note is the observation that even macrocyclic lactones can be formed in high yields without high dilution or other catalysts.

(3)

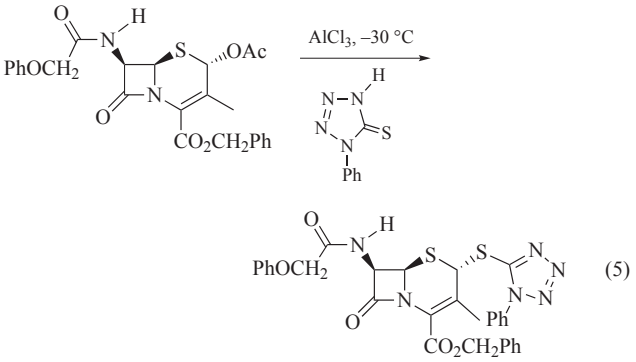
Peptide Formation. Amino acids can be coupled to form amides using this technology.[2] A nitrogen-protected amino acid is activated and allowed to react with a carboxylate-protected amino acid, thus forming the peptide linkage. The reagent can be recovered unchanged at the end of either of these sequences.

Sulfur Nucleophile. The nucleophilic nature of the sulfur in 1-phenyl-2-tetrazoline-5-thione can be utilized for the introduction of sulfur into organic compounds. Thus Mitsunobu reaction of a protected sugar with the reagent affords the substituted sugar (eq 4).[3]



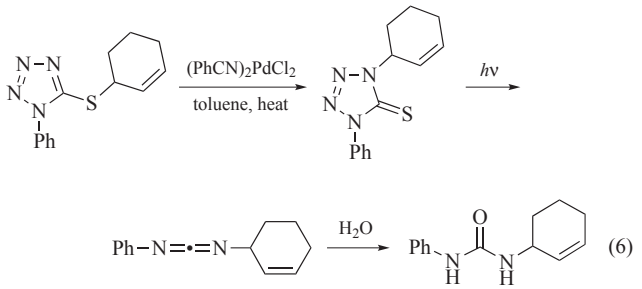
(4)

In a similar fashion, substitution of a cephalosporin could be achieved (eq 5).[4]



(5)

Alkylation at nitrogen (or redirected to nitrogen) affords the substituted tetrazolinethione. Under photolysis conditions, such compounds undergo loss of sulfur and nitrogen to afford the carbodiimide (eq 6),[5] subsequent hydrolysis providing the urea.



First Update

Milan Bruncko
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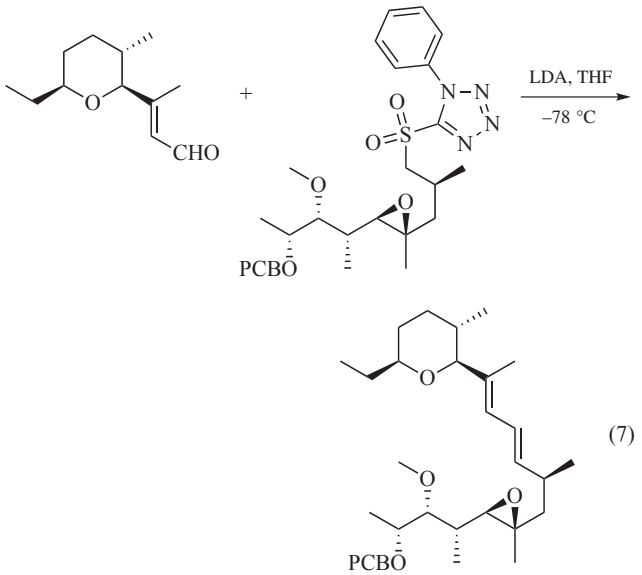
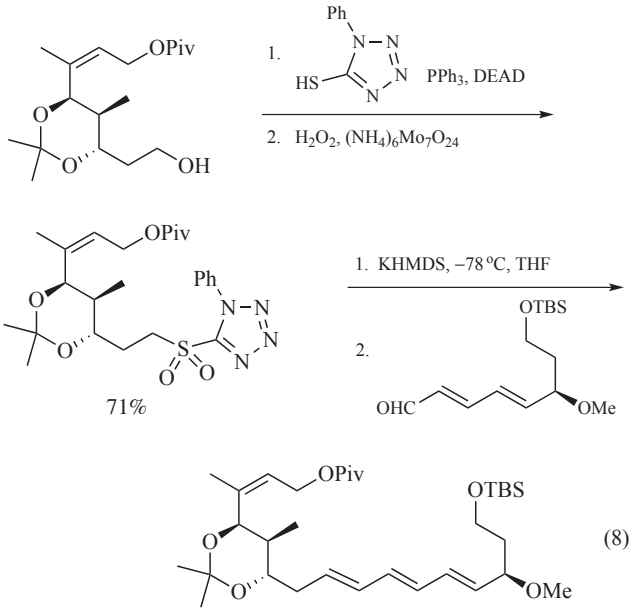
Olefination. One of the most important applications of alkyl-2-sulfonyl-1-phenyl-1*H*-tetrazoles, formed by nucleophilic displacement of a suitable leaving group by 1-phenyl-2-tetrazoline-5-thione followed by sulfur oxidation, is the Kocienski-Julia type olefination reaction that is extensively used in the synthesis of many natural products. Alkenes formed in this manner are produced with excellent *E*-stereoselectivities and in high yields. The *E*/*Z* ratio is influenced by choice of both polarity and coordinating ability of the solvent (increases from DME>THF>Et_2O>toluene), and by counter ion (K>Na>Li).[6] For example, Kocienski and co-worker utilized this methodology in a key step involving coupling of two herboxidiene fragments (eq 7).[7]



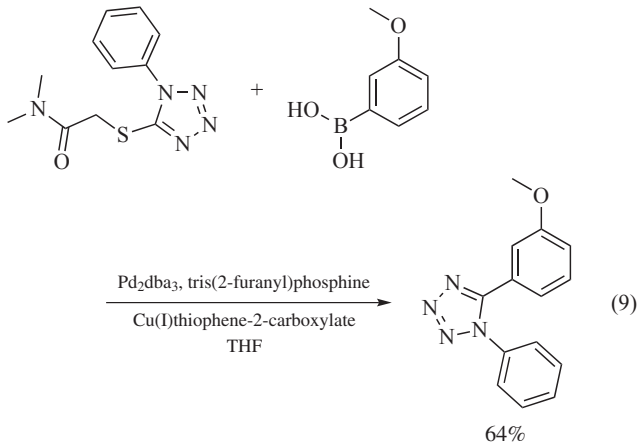
81% (*E*/*Z* 91:9)

In a further example, Smith and Wan exploited the nucleophilic capability of 1-phenyl-2-tetrazoline-5-thione in the Mitsunobu reaction, followed by oxidation to the sulfone with hydrogen peroxide and ammonium heptamolybdate tetrahydrate as a key step in a synthesis of the ansamycin antiobiotic, (+)-thiazinotrienomycin-E (eq 8).[8] Importantly, use of the phenyltetrazolylthione-derived sulfone gave an *E*/*Z* ratio of 10:1 in this coupling whereas the more conventional benzthiazole-2-thiol-derived system resulted in a selectivity of only 1.5:1 in favor of the *E*-isomer.



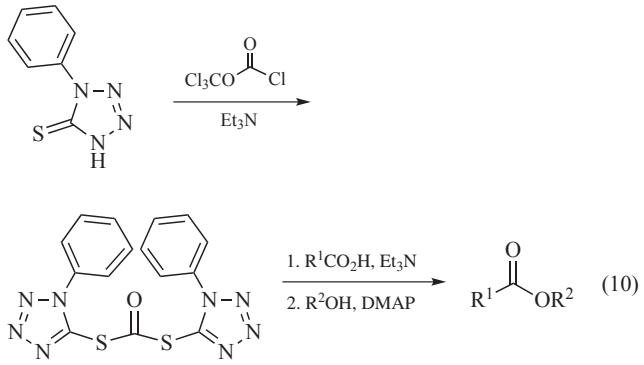
85% (*E*/*Z* 10:1)

Suzuki Coupling. 1-Phenyl-2-tetrazolyl-5-thioethers have been employed in modified Suzuki couplings when they serve as donors of the phenyltetrazolyl moiety. The coupling of the thioether and a boronic acid was catalyzed by Pd_2dba_3/tris(2-furanyl)phosphine with assistance of 1.2 equiv of Cu(I)-thiophene-2-carboxylate (eq 9).[9]



64%

Esterification. Treatment of 1-phenyl-2-tetrazoline-5-thione with trichloromethyl chloroformate forms the symmetrical dithiocarbonate. This stable, crystalline solid acts as a novel reagent for the one-pot esterification of acids (eq 10).



(10)

Related Reagents. Benzthiazole-2-thiol; 1-*tert*-butyl-1*H*-2-tetrazoline-5-thione.

Second Update

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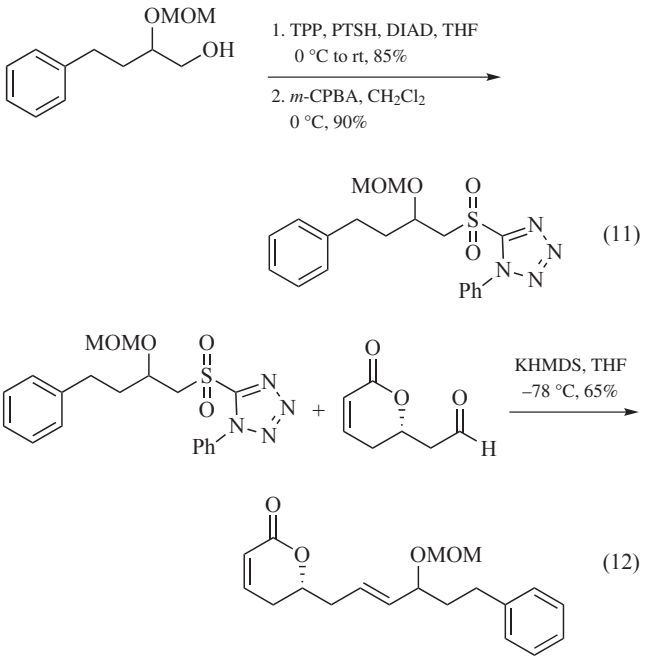
University of Iowa, Iowa City, IA, USA

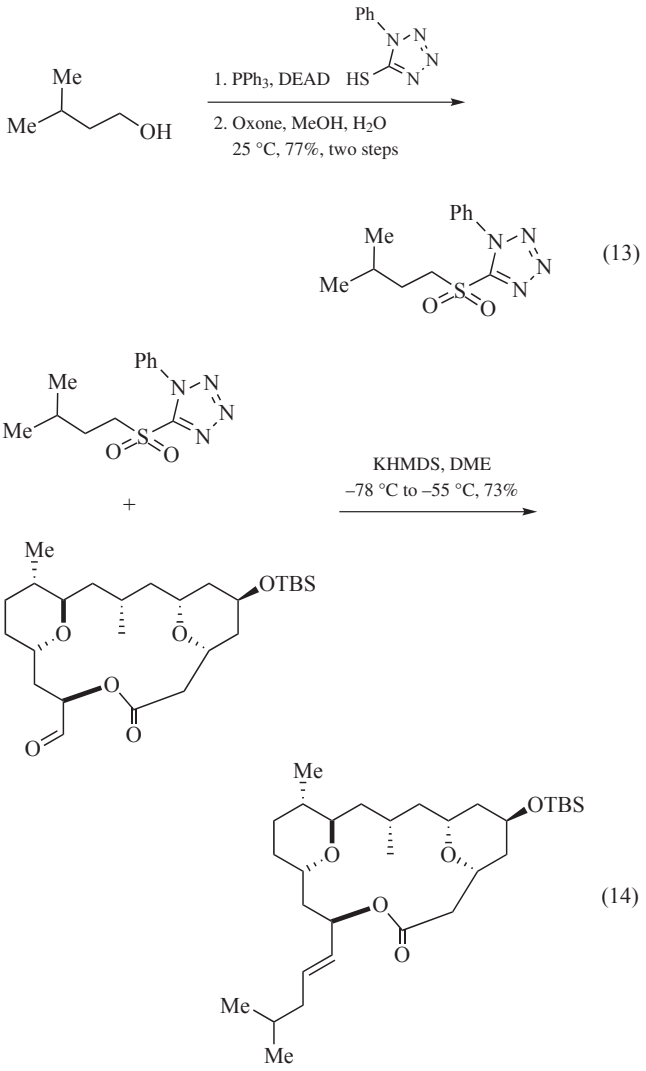
Olefination. 2-Sulfonyl-1-phenyl-1*H*-tetrazole was employed in the total synthesis of (*R*)-rugulactone. The alcohol was converted to the sulfide using the Mitsunobu conditions. The corresponding sulfone was obtained by oxidizing the sulfide with *m*-CPBA (eq 11). The crude aldehyde reacted with sulfone in the presence of KHMDS to afford the desired alkene using the Julia–Kocienski olefination (eq 12).[11]



(11)

(12)

Fettes and Carreria performed the Mitsunobu reaction on alcohol and 2-sulfonyl-1-phenyl-1*H*-tetrazole to obtain the sulfide that was oxidized to the corresponding sulfone in the presence of oxone (eq 13). The sulfone was used to perform the Julia–Kocienski olefination to introduce the alkene side chain to the aldehyde in high yields (eq 14).[12]



(13)

(14)

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