t-Butylation of 5-Substituted Tetrazoles

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Received November 14, 1975

J. Heterocyclic Chem., 13, 391 (1976).

In the course of other work, a need arose for a method to block the 1- or 2-position on the tetrazole ring, prior to reaction on substituents at the 5-position, to be followed by an easy, uncomplicated removal of the protective blocking group. Although this can be accomplished through *N*-benzylation with subsequent removal of this group by catalytic debenzylation over Pd (1), such an approach was not a suitable solution to this problem. It was found that the desired result could be realized by making use of the 1- or 2-*t*-butyl derivatives; the *t*-butyl group can be readily removed by dissolving the compound in concentrated sulfuric acid, a medium in which the tetrazole ring is moderately stable. 1-*t*-Butyl-5-phenyltetrazole was earlier prepared (2) by the thermal decomposition-rearrangement of $C_6H_5C(N_3)_2C(CH_3)_3$, which in turn was made from the corresponding dichloro compound and sodium azide. This method obviously has very restricted utility.

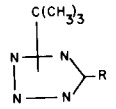
A simpler, more general procedure, which gives satisfactory yields (50-100%) of the mixed 1- and 2-isomers, is based on Vowinkel's method (3) for *t*-butylation of phenols: neat *t*-butyl alcohol and dicyclohexylcarbodiimide are condensed in the presence of cuprous chloride; this product and the 5-substituted tetrazole then react in dichloromethane to give the poorly soluble *N,N'*-dicyclohexylurea and the soluble *t*-butylated tetrazoles. Yields and properties of several compounds made in this manner are summarized in Table I.

EXPERIMENTAL

The following procedure is representative. Dicyclohexylcarbodiimide (30.6 g., 0.15 mole), *t*-butyl alcohol (12.4 g.), and cuprous chloride (300 mg.) were stirred under a calcium chloride drying tube for 5 days at room temperature. This reaction product was diluted with 175 ml. of dichloromethane, cooled to

Table I

1- and 2-*t*-Butyl 5-Substituted Tetrazoles



Position of *t*-butyl group	R	Formula	M.p., °C (b.p., °C, press)	Recrystallization solvent	% Yield	Analysis % C (theory)	% H (theory)	% N (theory)	% X (theory)
1	NH_2	$C_5H_{11}N_5$	193-194	2-propanol	40	42.26	7.72	50.03	--
2	NH_2	$C_5H_{11}N_5$	116-117	cyclohexane (a)	58	42.59 (42.53)	7.46 (7.86)	49.87 (49.61)	--
1	C_6H_5	$C_{11}H_{14}N$	108-109 (b)	cyclohexane	15	65.26	6.90	27.81	--
2	C_6H_5	$C_{11}H_{14}N$	(90-100, 5 x 10^{-4} mm)	--	59	65.12 (65.32)	7.19 (6.98)	27.91 (27.70)	--
1	SCH_3	$C_6H_{12}N_4S$	92-93	*n*-hexane	19	41.91	7.05	32.58	18.52
2	SCH_3	$C_6H_{12}N_4S$		--	42	41.81 (41.85)	6.95 (7.02)	32.45 (32.54)	18.48 (18.58)
1	Cl	$C_5H_9ClN_4$	114-115	cyclohexane	21	37.16	5.62	35.10	22.08
2	Cl	$C_5H_9ClN_4$	(25, 1μ)	--	30	37.54 (37.39)	5.68 (5.65)	34.77 (34.89)	21.98 (22.08)

(a) Easily sublimed at 110-120°, 25 mm. (b) Reported reference 2, 102°.

5° and treated over 30 minutes with 21.8 g. (0.15 mole) of dried 5-phenyltetrazole. Since the reaction was exothermic, cooling was required to keep the temperature 5-10°. After stirring for 30 minutes more at 5°, the thick slurry was allowed to warm to 25° and stirred for 20 hours. The solid was then removed by filtration and washed twice with 50-ml. portions of dichloromethane. (Extraction of this solid with aqueous sodium hydroxide to remove 8.9 g. of unreacted 5-phenyltetrazole left 32.3 g. of dicyclohexylurea, m.p. 230°.)

The combined dichloromethane solutions were shaken with 100 ml. of water and enought 30% aqueous sodium hydroxide to adjust the *p*H to the phenolphthalein endpoint (1.4 g. more of 5-phenyltetrazole removed), separated, washed with 100 ml. of water, dried over anhydrous sodium sulfate, and evaporated; 15.4 g. of oil plus solid. This crude product was slurried with 60 ml. of *n*-pentane and 30 ml. of dichloromethane, filtered from more of the urea, diluted with 100 ml. of pentane and chilled first at 5°, then at -15°, for several days. The crystals of the 1-isomer (2.8 g., m.p. 100-105°) were removed; two recrystallizations from cyclohexane raised the m.p. to 108-109°. Evaporation of the pentane solution left 10.7 g. of oil which was distilled.

In the case of the 5-amino compound the reaction solvent was a 1:1 mixture of tetrahydrofuran-dichloromethane; benzene was used as the solvent for separating the 1-isomer (poorly soluble) from the 2-isomer (readily soluble).

Structures are assigned to the isomers on the basis that the 1-isomers are generally higher melting and less soluble than the corresponding 2-isomers (4).

Dealkylation of 1- and 2-*t*-Butyl-5-phenyltetrazole.

Heating 0.3 g. of unseparated, mixed isomers with 1 ml. of concentrated sulfuric acid on the steam bath for 2 hours (gas evolution), diluting with 8 ml. of water, cooling to 5°, filtering, washing and drying gave 0.21 g. (98%) of base soluble material, m.p. 213-215°. The extent of dealkylation was only about 12% after 3 hours at 25°.

REFERENCES AND NOTES

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