A New Route to 1-Alkyltetrazoles: *via* 2-*tert*-Butyltetrazoles

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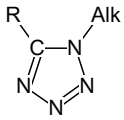
1-Alkyl-5-R-tetrazoles, free of the corresponding 2-isomers, can be readily obtained in high yield from 5-R-tetrazoles *via* exhaustive alkylation of their readily available 2-*tert*-butyl derivatives followed by removal of the *tert*-butyl group from the 1(4)-alkyl-3(2)-*tert*-butyl-5-R-tetrazolium salts formed.

The chemistry of tetrazoles is an area of extensive study, since tetrazoles attract both theoretical and practical interest. The former stems from the extremal properties of the tetrazole ring as the last stable representative of the series of azoles, and the latter is caused by the considerable utility of tetrazole compounds in medicine, biology, agriculture and various fields of technology.[1] Nowadays, there are a number of methods known for the direct formation of the 1-alkyl-substituted tetrazole ring.[1] Most of these syntheses deal with solutions of toxic and hazardous hydrazoic acid and/or with reagents of limited availability, such as isonitriles, nitrilium salts, orthocarboxylic acid esters, *etc*. Alkylation[2] of tetrazole and 5-monosubstituted tetrazoles therefore remains one of the most useful routes for the preparation of their 1-alkyl derivatives due to the availability of various starting tetrazoles and alkylating agents and to the simplicity of the process. However, this reaction provides, as a rule, mixtures of isomeric 1- and 2-alkylated tetrazoles (**1** and **2**, respectively), the latter often being the major products.[1–4]



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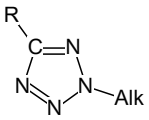

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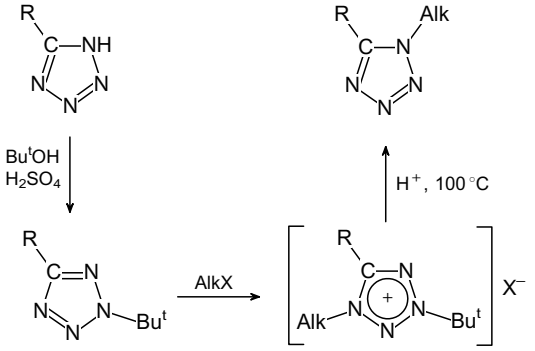
Attempts have been made to change the alkylation direction in favour of 1-isomer formation by preliminary protective blocking of the N2 site with the tri-*n*-butylstannyl group,[4] which is removed during alkylation, or by bringing into the reaction tetrazoles as complexes of the type $(PBu^n_3)Co(DH)_2$(5-R-tetrazolate),[5] where DH is the monoanion of dimethylglyoxime. In such structures the N2 position of the heterocycle appears to be spatially blocked by the oxime ligands against alkylation. None of these approaches are sufficiently convenient in practice, since the former fails to supress completely the N2-alkylation,[4] while the latter provides small yields and entails difficulties both in the isolation of the products and in the synthesis of the starting complexes.[5]

We have now developed a new, facile synthesis for 1-alkyl-5-R-tetrazoles, represented here by Scheme 1.† The method is based on the next general considerations, which correspond to the steps shown:



Scheme 1

(i) NH-tetrazoles can be converted easily and quantitatively into their 2-*tert*-butyl derivatives by means of regioselective N2-alkylation in a highly acidic medium;[6]

(ii) when they interact with alkylating agents, 2-substituted tetrazoles undergo exhaustive alkylation exclusively at the N4 position of the heterocycle, 1(4),3(2)-substituted tetrazolium salts being formed;[4,7]

(iii) the *tert*-butyl group can be readily removed from the N-positions of the tetrazole ring under relatively mild conditions.[3]

Thus, the recently discovered reaction of N2-regioselective alkylation of tetrazoles[6] opens up a new convenient synthetic pathway to 1-alkyltetrazoles too. This approach provides undoubted isomeric purity and gives high yields using readily available reagents under mild conditions.

It should be noted, however, that 2-*tert*-butyltetrazoles do not react under the conditions stated here with such alkylating agents as alkyl halides.

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Table 1 Synthesis of 1-Alkyl-5-R-tetrazoles (Scheme 1).

R	Alk	AlkX	Isolated yield (%)
H	Me	Dimethyl sulfate	94
H	Me	Methyl benzenesulfonate	90
H	Et	Triethyloxonium tetrafluoroborate	86
H	Bu^n	*n*-Butyl *p*-toluenesulfonate	88
Me	Me	Dimethyl sulfate	92
Ph	Me	Dimethyl sulfate	98
CF_3	Me	Dimethyl sulfate	83
$H_2C{=}CH$	Me	Dimethyl sulfate	78

† A typical experimental procedure for the synthesis of 1-alkyl-5-R-tetrazoles is as follows. To a solution of 2-*tert*-butyl-5-R-tetrazole[6] (30 mmol) in 30 ml of dry chloroform or ethyl acetate was added 36 mmol of alkylating agent (containing the required alkyl group, see Table 1) and the mixture was stirred with refluxing at 55–60 °C for 5 h. The solvent was then removed under reduced pressure, the residue was dissolved in 60 ml of concentrated hydrochloric acid and the solution was heated on a steam bath for 5 h. After being cooled, the reaction mixture was neutralized by aqueous NaOH and the product was extracted with methylene dichloride (3×25 ml). The combined extracts were washed with water, dried over anhydrous $MgSO_4$ and solvent was removed. At this stage all products were tested by TLC and ^{1}H NMR spectroscopy to confirm the absence of 2-isomers. The 1-alkyl-5-R-tetrazoles obtained were recrystallized from the appropriate solvents or distilled *in vacuo*, having characteristics consistent with the literature data.[2,8–10] Yields are listed in Table 1.

References

1 R. N. Butler, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 5, p. 791.

2 R. J. Spear, *Aust. J. Chem*., 1984, **37**, 2453, and references 2–32 cited therein.

3 R. A. Henry, *J. Heterocycl. Chem.*, 1976, **13**, 391.
4 T. Isida, T. Akijama, K. Nabika, K. Sisido and S. Kozima, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 2176.
5 N. E. Takach, E. M. Holt, N. W. Alcock, R. A. Henry and J. H. Nelson, *J. Am. Chem. Soc.*, 1980, **102**, 2968; N. E. Takach and J. H. Nelson, *Inorg. Chem.*, 1981, **20**, 1258.
6 A. O. Koren and P. N. Gaponik, *Khim. Geterotsikl. Soedin.*, 1990, 1643 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1990, 1366].
7 A. B. Zhivich, G. I. Koldobskii and V. A. Ostrovskii, *Khim. Geterotsikl. Soedin.*, 1990, 1587 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1990, 1319]; P. N. Gaponik, O. A. Ivashkevich, V. N. Naumenko, T. B. Kovalyova, T. N. Andreeva and A. O. Koren, *Spectrochim. Acta, Part A*, 1993, **49**, 135.
8 W. G. Finnegan and R. A. Henry, *J. Org. Chem.*, 1959, **24**, 1565.
9 P. N. Gaponik, O. A. Ivashkevich, O. N. Bubel', M. M. Degtyarik and V. N. Naumenko, *Teor. Eksp. Khim.*, 1989, 33 (in Russian).
10 R. A. Henry, *US Patent* 3351627, 1967.

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