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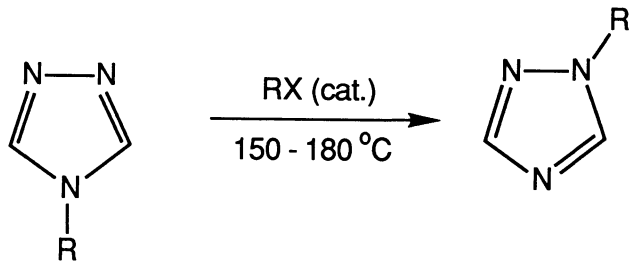
Regiospecific Synthesis of 1-Substituted 1,2,4-Triazoles Involving Isomerization of the Corresponding 4-Substituted Compounds

Keith SMITH,* Andrew SMALL, and Michael G. HUTCHINGS†
Department of Chemistry, University College of Swansea, Swansea, SA2 8PP, U.K.
†ICI Colours and Fine Chemicals, Fine Chemicals Research Centre, Blackley, Manchester M9 3DA, U.K.

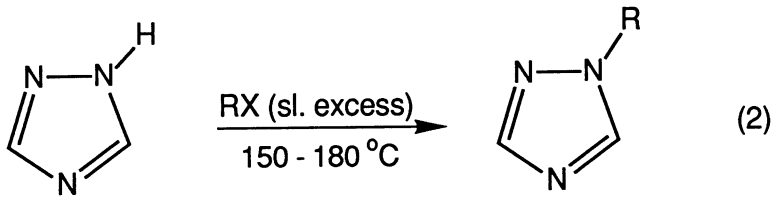
On heating with a catalytic quantity of the corresponding alkyl or phenacyl halides, 4-alkyl- or 4-phenacyl-1,2,4-triazoles isomerize *via* quaternary salts to their 1-substituted isomers. Thus, the 1-substituted compounds can now be obtained regiospecifically from 1,2,4-triazole by alkylation-isomerization.

Many 1-substituted-1,2,4-triazoles are important to the pharmaceuticals and agrochemicals industries,[1] since they show fungicidal, herbicidal, plant growth regulatory and other useful properties. Unfortunately, the synthesis of such compounds *via* direct alkylation of 1,2,4-triazole frequently produces a mixture[2] in which the 1-isomer (**2**) is contaminated with 3 - 30% of the 4-isomer (**1**) and removal of the unwanted isomer may be difficult or expensive to achieve. We now report that 4-alkyl- and 4-phenacyl-1,2,4-triazoles (**1**) readily isomerize to their 1-substituted analogues (**2**) on heating with a catalytic quantity of the corresponding organic halides (Eq. 1).



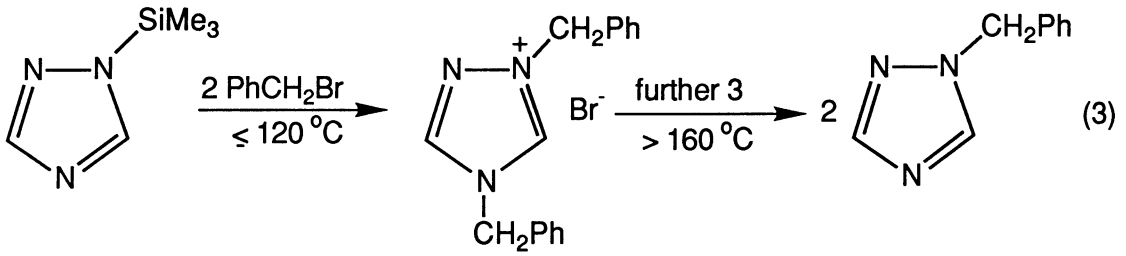
1 **2** (1)

Alternatively, the 1-isomer can be obtained regiospecifically by direct alkylation of 1,2,4-triazole at elevated temperatures with a slight excess of alkylating agent (Eq. 2). The reactions proceed through the intermediacy of quaternary salts.



(2)

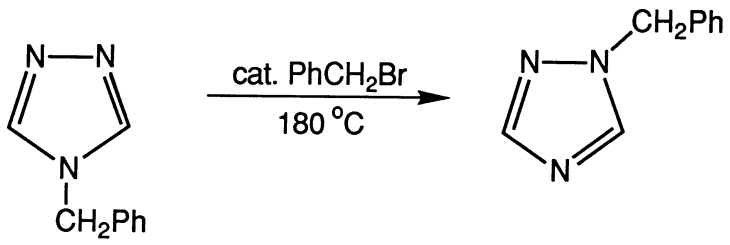
In the course of our attempts to find a regiospecific approach to 1-substituted triazoles we were attracted by literature accounts which reported that 1-trimethylsilyl-1,2,4-triazole (**3**)[3] and 1-tributylstannyl-1,2,4-triazole[4] react regiospecifically with halogenoalkanes and α-halogenocarbonyl compounds to give high yields of the corresponding 1-substituted derivatives. However, in our hands the reaction of benzyl bromide with **3** under the stated conditions (10 h at 120 ℃)[3] gave less than a 20% yield of 1-benzyl-1,2,4-triazole (**5**) and even this was contaminated with its 4-substituted isomer (**6**). The major product was a quaternary salt (**4**), the possible formation of which is specifically rejected in the original literature report.[3] Details of the procedure for isolation of **5** from this reaction are not recorded in the report.[3] However, by analogy with an earlier procedure[4] it appeared likely that isolation involved distillation of the reaction mixture at 162-164 ℃/18 mmHg. Indeed, distillation of our reaction mixture under such conditions provided a good yield of pure **5**, probably by the route shown in Eq. 3.



(3)

3 **4** **5**

Moreover, **5** was also produced regiospecifically and in high yield by reaction of unsubstituted 1,2,4-triazole with benzyl bromide at 180 ℃, thus demonstrating that the trimethylsilyl group is not essential for the reaction. Furthermore, a mixture of **4**, **5**,and **6** was again produced when triazole and benzyl bromide were heated to 110 ℃. This discovery opened up the possibility that **6** could be isomerized to its 1-isomer by heating together with a small amount of benzyl halide (Eq. 1). This proved to be the case. Compound **6** was converted into a mixture containing **5** (94%) and **6** (6%) on heating at 180 ℃ for 2.5 h with 3.3 mole per cent of benzyl bromide (Eq. 4). Further heating converted the remaining **6** into **5**, with *ca.* 3% of the salt (**4**) present as the only significant impurity at the end of the reaction. The reaction worked equally well with benzyl chloride as the catalyst and *N*-methylpyrrolidone could also be used as a solvent without detriment.



(4)

6 5

A number of other 4-alkyl- and 4-phenacyl-1,2,4-triazoles were subjected to the isomerization reaction (Eq. 1) in order to test its generality. The results are recorded in Table 1.

Table 1. Conversion of 1 into 2 via isomerization according to Eq. 1

R	X	mol% RX	Reaction conditions temp/°C, time/h	Product ratio 2:1 isomerization[a]	alkylation of triazole[b]
$PhCH_2$	Br	3.3	180, 5	>98:<2	(88:12)
n-C_6H_{13}	I	15	160, 40[c]	92:8	(86:14)
PhCH(Me)	Br	6	160, 22[c]	>97:<3	(89:11)
$PhCOCH_2$	Cl	14	180, 7	>99:<1	(87:13)
"	"	10	150, 30[c]	92:8	(")
4-$ClC_6H_4COCH_2$	Cl	16	170, 2.5[c]	>99:<1	(91:9)
4-$FC_6H_4COCH_2$	Cl	20	160, 1[c]	>99:<1	(92:8)
4-$BrC_6H_4COCH_2$	Br	5.7	160, 3[c]	>99:<1	(91:9)

a) Proportions in the crude product mixture after isomerization of pure 4-isomer (1). The proportions were determined by NMR, hplc or gc as appropriate. In addition to 2 and 1 there was also present a quantity of quaternary salt corresponding to the amount of catalyst added. The amount of catalyst was determined by the quantity present in a single small addition since reactions were carried out on a very small scale.

b) The proportions obtained on direct alkylation of 1,2,4-triazole under moderate conditions (our results), reported for comparison.

c) These reactions were carried out in the presence of a minimal quantity of *N*-methylpyrrolidone as solvent. Other reactions were carried out without solvent.

It is clear that isomerization of 4-alkyl- and 4-phenacyltriazoles is a general process, and gives rise consistently to the more stable 1-substituted isomers. We have made no attempt to optimize individual reactions, but it appears that heating for several hours at 160-180 ℃, in the presence of a few per cent of the corresponding halide, is sufficient to allow almost complete isomerization in most cases. In the case of 4-phenacyl-1,2,4-triazole we have carried out the reaction on a larger scale and isolated the product. 1-Phenacyl-1,2,4-triazole was obtained pure in 64% isolated yield after chromatography on silica and recrystallisation.

These results now offer two possibilities for improvement in recovery of 1-substituted-1,2,4-triazole products from alkylation reactions of 1,2,4-triazole: (1) the reaction can be carried out with excess halide and the mixture heated directly to *ca.* 180 ℃ so that isomerization takes place prior to isolation; or (2) the initial reaction can be carried out at lower temperature, the mixture can be separated to give pure 1-substituted compound, and the residue, which is rich in 4-isomer, can then be isomerized.

These results have obvious commercial potential for the synthesis of 1-substituted 1,2,4-triazoles.[5] It is also likely that similar isomerizations are possible for imidazoles and related compounds.

We thank the S.E.R.C. for a CASE studentship (to AS).

References

1) See, for example, P.A. Worthington, "A.C.S. Symposium Series No. 355 - Synthesis and Chemistry of Agrochemicals," American Chemical Society (1987), Chap. 27, p. 302.

2) Esters of phosphonic and phosphinic acids are reported to alkylate 1,2,4-triazole regiospecifically, but in low yield: M. Hayashi, K. Yamauchi, and M. Kinoshita, Bull. Chem. Soc. Jpn., 49, 283 (1976). For a review of 1,2,4-triazole chemistry, see C. Temple, "Triazoles 1,2,4," in "The Chemistry of Heterocyclic Compounds," ed by J.A. Montgomery, John Wiley and Sons, New York (1981), Vol. 37. It is possible to synthesize 1-alkyltriazoles regiospecifically *via* approaches which do not involve simple alkylation of 1,2,4-triazole itself; see, for example, B.A. Astleford, G.L. Goe, J.G. Keay, and E.F.V. Scriven, J. Org. Chem., 54, 731 (1989).

3) J.P. Gasparini, R. Gassend, J.C. Maire, and J. Elguero, J. Organomet. Chem., 188, 141 (1980).

4) R. Gassend, J.C. Maire, and J.-C. Pommier, J. Organomet. Chem., 133, 169 (1977).

5) A patent application has been made in respect of the new process: M.G. Hutchings, A. Small, and K. Smith, G.B. Patent Appl. 2 198 436A (publ. Jun. 15 1988; priority date Dec. 4 1986). During the course of preparation of this manuscript another patent dealing with essentially the same process has appeared: C.S. Barnum, E.R. Olson, and W.K. Moberg, Eur. Pat. Appl. 0 296 745 (publ. Dec. 28 1988; priority date Jun. 16 1987).

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