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Regiospecific Synthesis of 1-Substituted 1,2,4-Triazoles by Reaction of 1,2,4-Triazole with Aldehydes

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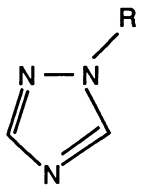
The reactions of 1,2,4-triazole with aldehydes and various acid chlorides provide a convenient, regiospecific route to 1-substituted 1,2,4-triazoles.

The 1-substituted 1,2,4-triazole unit (**1**) is an important constituent of many agrochemicals, particularly fungicides and plant growth regulators, and pharmaceuticals. It is generally introduced by reaction of 1,2,4-triazole with an alkylating agent, of which various types have been used.[1] Unfortunately, many of these reactions are limited by the simultaneous formation of the unwanted and biologically inactive 4-isomer (**2**), which can be particularly problematic on a manufacturing scale. Thus, methods for *regiospecific* substitution of 1,2,4-triazole are much needed. In the preceding communication we report a method for achieving this goal by isomerization of 4-substituted 1,2,4-triazoles at elevated temperatures in the presence of the corresponding alkyl or phenacyl halides.[2] We now report a second method, which is useful for the synthesis of 1-(1-acyloxyalkyl)-1,2,4-triazoles (**3**).



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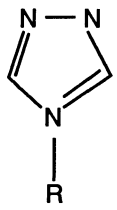

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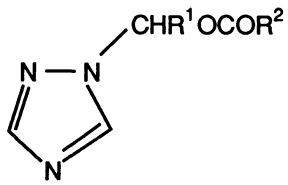
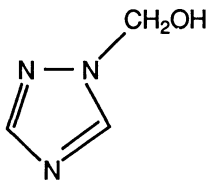


3

The patent literature records the regiospecific formation of hemiaminal products (**4** and **5**) on reaction of 1,2,4-triazole with formaldehyde[3] and chloral,[4] respectively. However, these aldehydes can be regarded as special cases. For example, both form relatively stable adducts with water whereas most simple aldehydes of the form RCHO and ArCHO do not. It was therefore of interest to see if hemiaminal formation would occur on reaction of 1,2,4-triazole with other aldehydes, and if this could provide a general regiospecific approach to useful 1-substituted triazole derivatives.



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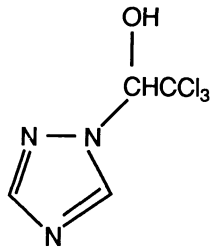
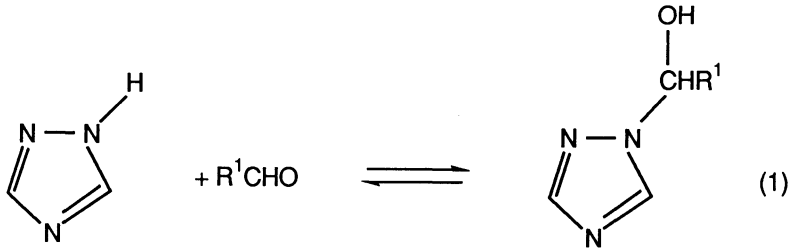


5

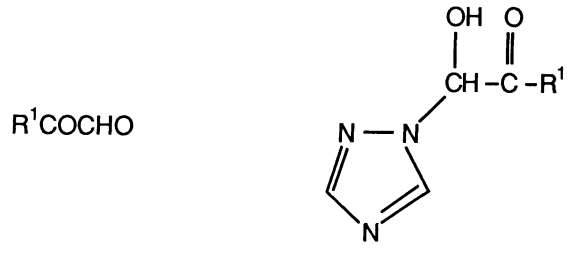
Proton NMR spectra of 1:1 mixtures of simple aliphatic aldehydes (e.g. butanal) and 1,2,4-triazole revealed the presence of two new triazole signals of equal intensity, indicating the formation of 1-(1-hydroxyalkyl)-1,2,4-triazole (**6**), along with a smaller peak at a chemical shift value corresponding to unreacted triazole. Addition of excess aldehyde caused an increase in the intensity of the two peaks due to **6** and a decrease in the triazole peak. Conversely, dilution of the solution with deuteriochloroform caused a decrease in the intensity of the two peaks due to **6** and an increase in the triazole peak. This behaviour is consistent with the existence of the equilibrium shown in Eq. 1.



(1)

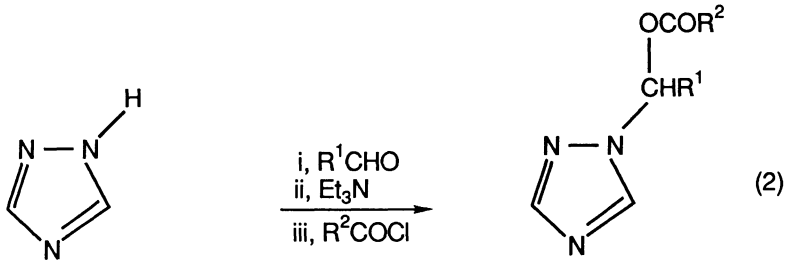
6

Addition of two equivalents of butanal to one of triazole resulted in the formation of **6** (R^1 = *n*-Pr) in *ca.* 95% yield at ambient temperature, according to NMR. For the more hindered pivaldehyde the yield of hemiaminal (**6**, R^1 = *tert*-Bu) was only *ca.* 60% under comparable conditions, while aromatic aldehydes and all types of ketones showed no evidence for hemiaminal formation. By contrast, electronegatively substituted aldehydes of type **7** (R^1 = *tert*-Bu, Ph) gave stable hemiaminals (**8**), which could be isolated. Attempts to isolate the hemiaminal from *n*-butanal by evaporation of the excess aldehyde resulted in eventual removal of all the aldehyde and the recovery of 1,2,4-triazole.[5)]



7 8

In an attempt to trap **6** as a stable, isolable derivative a mixture of triazole and butanal was treated with acetyl chloride and triethylamine (Eq. 2). 1-(1-Acetoxybutyl)-1,2,4-triazole (**3**, R^1 = *n*-Pr, R^2 = CH_3) could easily be isolated from the reaction mixture and appeared to be completely free of any 4-substituted analogue. The yield of **3** was found to be highly dependent on the reaction conditions. A good yield of **3** (R^1 = *n*-Pr, R^2 = CH_3) was obtained when the initial additions of triethylamine and acetyl chloride were carried out slowly, with stirring, at low temperature (*ca.* -20 ℃), and the reaction mixture was then allowed to warm up to ambient temperature and stirred for one week.



(2)

This procedure was therefore applied to a range of different aldehydes (Table 1). Good yields of **3** were obtained from a variety of aliphatic aldehydes, including sterically hindered ones. More notably, *the method also works for aromatic aldehydes* for which there is no NMR evidence for formation of the hemiaminal (**6**). In no case was there evidence for production of any of the corresponding 4-isomer. Furthermore, other acylating agents, such as pivaloyl chloride and benzoyl chloride, could also be used as trapping agents. For example, compounds (**3**; R^1 = *iso*-Pr, R^2 = Ph; R^1 = R^2 = Ph; R^1 = *iso*-Pr, R^2 = *tert*-Bu; R^1 = *p*-ClC_6H_4, R^2 = *tert*-Bu) could all be obtained without problem. Thus, this approach provides a general, regiospecific route to 1-(1-acyloxyalkyl)-1,2,4-triazoles of type **3** (R^1, R^2 = alkyl or aryl). These, and related compounds, should prove to be valuable intermediates in the synthesis of other triazole derivatives, including commercially important ones. In this context, derivatives of the hemiaminal (**8**) are particularly promising intermediates for the synthesis of triazole derivatives of known biological activity, especially where R^1 is *tert*-Bu or aryl.

The mechanistic details of the reaction have yet to be fully elucidated. However, our evidence to date indicates that the reaction does *not* proceed simply *via* reaction of the hemiaminal (**6**) with the added acyl chloride. We are carrying out further mechanistic investigations, and continuing to explore and extend the scope of the reactions. Early indications suggest that the reaction is applicable to pyrazole and imidazole derivatives.

Table 1. Synthesis of 1-(1-acetoxyalkyl)-1,2,4-triazoles (**3**, $R^2 = CH_3$)

R^1	Yield of **3** ($R^2 = CH_3$)/%[a)]
CH_3	82
CH_3CH_2	73
$CH_3CH_2CH_2$	69
$CH_3CH_2CH_2CH_2$	82
$(CH_3)_2CH$	77
$(CH_3)_3C$	59
Ph	46
p-$MeOC_6H_4$	45
p-ClC_6H_4	43
p-MeC_6H_4	46
o-ClC_6H_4	43
m-$NO_2C_6H_4$	42

a) Yield of isolated product following reaction under the standard conditions described in the text. No attempt was made to optimize individual reactions, though higher yields have been obtained in some cases under different conditions.

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References

1) 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.

2) K. Smith, A. Small, and M. G. Hutchings, preceding communication.

3) W. Kunz and L. Maier, Eur. Patent 82810057.4 (4.3.82).

4) A. Hubele, Swiss Patent 586 011 (20.12.1974); Ger. Offenlegungsschrift 25 06 598 (17.2.75)

5) During the course of this work a patent appeared which records the formation of 1-(1-chloroethyl)-1,2,4-triazole from the hemiaminal (**6**, $R^1 = CH_3$) (Ref. 6). This hemiaminal is reputedly obtained by evaporation of excess acetaldehyde from a reaction of the type indicated by Eq. 1. Our experience suggests that extreme care would be needed to avoid total removal of acetaldehyde by such a procedure, and that in any case the hemiaminal thus obtained would be contaminated by both triazole and acetaldehyde because of the existence of the equilibrium shown in Eq. 1.

6) R. Thomas, J. Stetter, B. Homeyer, and B. Becker, Ger. Offenlegungsschrift DE 3438919 A1 (24.10.84; published 24.4.86)

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