Acid-Mediated Regioselective Alkylation of 1,2,3-Triazole

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Received April 26, 2002

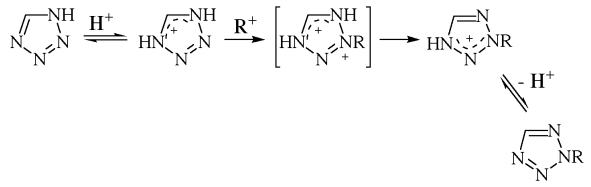
1,2,3-Triazole reacts with isopropyl alcohol in concentrated sulfuric acid to yield 1-isopropyl-1*H*-1,2,3-triazole as the only reaction product.

J. Heterocyclic Chem., **39**, 1111 (2002).

To date, *N*-alkylation of an existing heterocycle remains the most common and straightforward and, in many cases, the only synthetic pathway to various *N*-alkyl triazoles and tetrazoles. However, alkylation of *N*-unsubstituted tetrazoles, 1,2,4- and 1,2,3-triazoles under basic, neutral, and weakly acidic conditions is inherently not regiospecific, and generally yields mixtures of isomeric *N*-alkyl derivatives [1–3]. This simultaneous production of regioisomers, necessitating their subsequent separation, has been a weak point of synthetic methods involving *N*-alkylation and a driving force behind developing circumventive techniques [4–6].

Some time ago, we discovered and studied the reaction of regioselective alkylation of *N*-unsubstituted tetrazoles by alcohols and olefins in media of high acidity [7–10]. This reaction was found to exploit peculiarities of protonation of the tetrazole cycle and proceed by the mechanism depicted in Scheme 1.

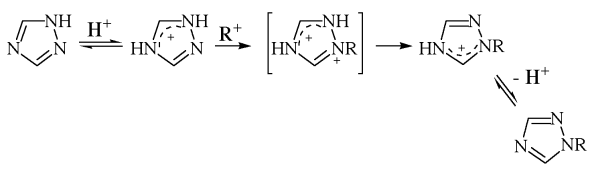
Scheme 1



In essence, the regioselectivity of alkylation here is due to the fact that tetrazoles enter the reaction in the protonated form, *i.e.* as 1*H*,4*H*-tetrazolium cations. In these substrates, the only site available for electrophilic attack is the nitrogen atom in position 2.

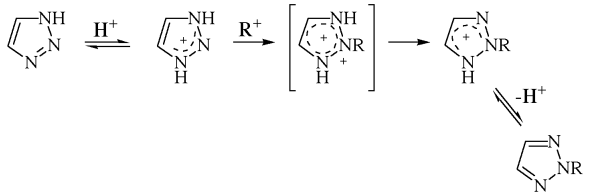
More recently, the scope of the regioselective alkylation in acidic media has been expanded to *N*-unsubstituted 1,2,4-triazoles [11,12]. While not yet substantiated experimentally, the process is believed to proceed according to Scheme 2, which essentially echoes Scheme 1.

Scheme 2



One could expect that *N*-unsubstituted 1,2,3-triazoles (which are known to form 1*H*,3*H*-1,2,3-triazolium cations upon protonation [3,13,14]) would follow the same pattern and would be regioselectively alkylated in media of high acidity to yield 2-alkyl derivatives, as shown in Scheme 3.

Scheme 3

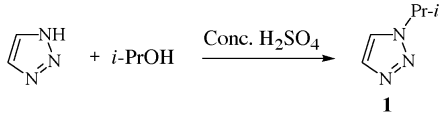


Closer examination of the protonated form of 1,2,3-triazole reveals, however, that it differs substantially from those of tetrazole and 1,2,4-triazole. Here, the nitrogen atom in position 2, the only site that could be available for substituent introduction, is intimately involved in distributing positive charge. Electrophilic attack at this atom is, therefore, unfavorable, and alkylation of 1*H*,3*H*-1,2,3-triazolium cations (Scheme 3) is unlikely to occur.

It has been shown that 1,2,3-triazole does undergo a regioselective alkylation in a highly acidic medium. Particularly, it reacts with isopropyl alcohol in concentrated sulfuric acid, the sole reaction product being, surprisingly, 1-isopropyl-1*H*-1,2,3-triazole (**1**, Scheme 4). An unambiguous structural assignment of the product was made based on the analysis of its NMR spectra in comparison with those of 1-methyl- and 2-methyl-1,2,3-triazole [6,15].

In contrast to the acid-mediated regioselective alkylation of tetrazoles and 1,2,4-triazoles, the reaction of 1,2,3-triazole is rather slow. Thus, isolated yield of **1** was only

Scheme 4



ca. 5% after 2 hours and 80% after 40 hours (*cf*. 80% after 70 minutes for 2-isopropyltetrazole [7] under identical reaction conditions, see Experimental).

There are two conceivable explanations for the dissimilarities in reaction courses and reactivities of 1,2,3-triazole and tetrazoles/1,2,4-triazoles, namely: 1) the mechanism of the *N*1-regioselective alkylation of 1,2,3-triazole in media of high acidity is different and/or more complex than those depicted in Schemes 1–3; or 2) the behavior of 1,2,3-triazole in media of high acidity is different and/or more complex than the formation of 1*H*,3*H*-1,2,3-triazolium cation.

Both of these hypotheses are currently being investigated and the results will be reported in due course.

EXPERIMENTAL

1-Isopropyl-1*H*-1,2,3-triazole (**1**).

To a stirred solution of 1,2,3-triazole (0.69 g, 10 mmol) in 95% sulfuric acid (7 mL), isopropyl alcohol (0.84 mL, 11 mmol) was added drop by drop for 10 minutes at room temperature. The reaction mixture was allowed to stand for 40 hours and was poured onto crushed ice (40 g). The resultant mixture was extracted with dichloromethane (4 x 10 mL). The combined extract was washed with saturated aqueous sodium hydrogencarbonate (2 x 5 mL) and water (2 x 5 mL), dried over anhydrous sodium sulfate, and gently evaporated under reduced pressure to yield **1** as a colorless liquid, 0.89 g (80%), bp 94-95 °C (3 mm Hg); ^{1}H nmr (300 MHz, deuteriochloroform): δ 1.60 (d, J = 6.7 Hz, 6H), 4.88 (sept, J = 6.7 Hz, 1H), 7.58 (s, 1H), 7.70 (s, 1H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 23.0, 52.7, 120.7, 133.5.

Anal. Calcd. for $C_5H_9N_3$: C, 54.03; H, 8.16; N, 37.81. Found: C, 54.10; H, 8.07; N, 37.85.

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