JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Acetylation of 5-Amino-1*H*-[1,2,4]triazole Revisited

ANETTA DŻYGIEL, ELŻBIETA MASIUKIEWICZ, AND BARBARA RZESZOTARSKA*

Institute of Chemistry, University of Opole, 48 Oleska Street, 45-052 Opole, Poland

The products of the acetylation reactions of the common herbicide 5-amino-1*H*-[1,2,4]triazole were investigated using HPLC, GC-MS, ^{1}H NMR, and FTIR spectroscopy. The conventional annular monoacetylation procedures with acetyl chloride are not regioselective and furnish a mixture of isomers. Traditional diacetylation in neat acetic anhydride under reflux produces a mixture of di-, mono-, and triacetylated derivatives. By using equivalent amounts of acetic anhydride in a dimethylformamide solution, a rapid and selective annular monoacetylation of 5-amino-1*H*-[1,2,4]triazole was achieved. The monoacetylation proceeds via the formation of the intermediate, 1-acetyl-3-amino-1*H*-[1,2,4]-triazole, which had not been observed previously and which undergoes transformation into the known 1-acetyl-5-amino-1*H*-[1,2,4]triazole. Neat acetic anhydride at room temperature affords the diacetylated derivative, 1-acetyl-3-(acetylamino)-1*H*-[1,2,4]triazole both from 5-amino-1*H*-[1,2,4]triazole itself and from either 1-acetyl-5-amino-*1H*-[1,2,4]triazole or 5-(acetylamino)-*1H*-[1,2,4]triazole. The atypical product of the second acetylation, 1-acetyl-5-(acetylamino)-1*H*-[1,2,4]triazole, has been identified. These results may be useful in the development of effective and selective preparative procedures for the acetylation of 5-amino-1*H*-[1,2,4]triazole.

KEYWORDS: 5-Amino-1*H*-[1,2,4]triazole; amino-[1,2,4]triazoles monoacetylated; amino-[1,2,4]triazoles diacetylated; 5-amino-1*H*-[1,2,4]triazole, acetylation of

INTRODUCTION

Amitrole (other names include Amizol, ATA, Cytrol, ENT, and Weedazol), usually called 3-amino-1*H*-[1,2,4]triazole, is a common, nonselective herbicide and defoliant for cotton (*1*−*3*). Efforts have been made toward anchoring it on polymer supports via acylation with polymeric anhydrides forming an amide bond(s), which in the case of an unequivocal product would allow for controlled release of the bioactive material under natural conditions (*4*, *5*). The amitrole molecule has three points to be N-acylated: the primary exocyclic NH_2 group and two annular *N*1 and *N*2 nitrogen atoms. The *N*4 nitrogen, like that of 1*H*-[1,2,4]triazole itself (*6*), offers significant resistance to acylation (*7*, *8*). Reactions with polymeric anhydrides do not appear to be selective *(4*, *5*). Therefore, more information is required about the various kinds of amitrole N-acylations. One way to attain this is to gain a better understanding of the acetylation of this compound. This might lead to development of better and higher yielding synthetic methods for the acetylation of amitrole. Such information would also be useful for biological studies, where acetylated radioisotopically labeled *C*-amino-[1,2,4]triazoles are necessary (*9*).

Amitrole as *C*-amino-[1,2,4]triazole belongs to a heterocyclic system, which can exist as one or more structural isomers differing only in the position of the H-atom. *Beilstein's Handbuch* lists all five possible structures of *C*-amino-[1,2,4]-triazole (cf. **Figure 1**) without indicating which of those is proper or prevalent (*10a*). However, in a later supplement of *Beilstein's Handbuch* (*10b*), *C*-amino-[1,2,4]triazole is named 3-amino-1*H*-[1,2,4]triazole. The basic preparative handbook *Organic Synthesis* (*11*) and most commercial catalogues (e.g., ref *12*) also list *C*-amino-[1,2,4]triazole as 3-amino-[1,2,4]-triazole, although no evidence for this structure is given. Calculations at a semiempirical level on the amino−imino tautomeric forms of *C*-amino-[1,2,4]triazole show 3-amino-1*H*-[1,2,4]triazole and 5-amino-*1H*-[1,2,4]triazole to be those most stable and evenly distributed. The remaining tautomers are unlikely to appear (**Figure 1**) (*13*). Recent ab initio calculations at the highest level of theory [6-31G**(CCSD)//6-31G** (HF)]

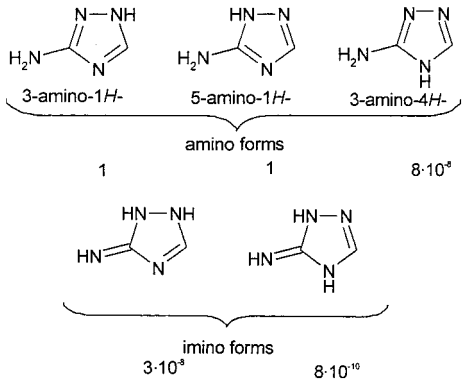

Figure 1. Probability of the occurrence of various *C*-amino-[1,2,4]triazole tautomers as anticipated by theoretical calculations (*13*).

* Author to whom correspondence should be addressed (e-mail rzeszot@uni.opole.pl; telephone 48 77 454 58 41, ext. 2232; fax 48 77 441 07 40).

10.1021/jf010734a CCC: $22.00
Published on Web 02/07/2002

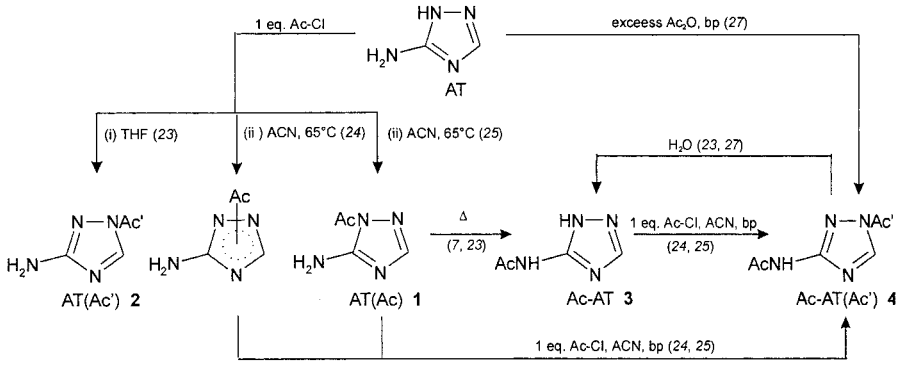

Figure 2. 5-Amino-1*H*-[1,2,4]triazole acetylation products with Ac-Cl or Ac_2O according to the literature (*7*, *23*–*25*, *27*).

Table 1. Chemical Shifts of 5-Amino-1*H*-[1,2,4]triazole (Obtained According to Reference *11*) in $DCON(CD_3)_2$

Compound	Temp. °C	Chemical shifts (ppm) bs, NH-ring	s, N-CH	bs, NH_2
Major set	-50	12.845 (16)[a]	7.516 (12)[a]	6.898 (12)[a]
Minor set	-50	13.485 (1)[a]	8.350 (1)[a]	5.980 (1)[a]
	20	12.200	7.401	6.004
			8.316 [b]	

[a] Numbers in parentheses denote a relative intensity of the signal. [b] Without integral.

on the three tautomeric amino forms of *C*-amino-[1,2,4]triazole also predict the 3-amino-1*H*- and 5-amino-1*H*- tautomers are essentially isoenergetic in the gas phase with the 3-amino-4*H*-tautomer 7 kcal mol^{-1} to higher energy (*14*). The electronic *Beilstein's Database* lists the same CAS Registry No. (61-82-5) for both 3-amino-1*H*- and 5-amino-1*H*- structures. X-ray diffraction on the single crystal of 3-amino-1*H*-[1,2,4]triazole (amitrole) (*15*) has revealed that it is actually 5-amino-1*H*-[1,2,4]-triazole (*16*). Likewise, in the solved crystal structures of *C*-amino-[1,2,4]triazole salts, the cation has the 5-amino-1*H*,4*H*-[1,2,4]triazolium form (e.g., refs *17*−*20*). The ^{13}C NMR spectrum of the commercially available *C*-amino-[1,2,4]triazole (*21*) in $(CD_3)_2SO$ solution shows this compound as being largely the 5-amino-1*H*- tautomer (*8*, *21*). A study 3-amino-1*H*-[1,2,4]-triazole in aqueous solution using ^{15}N NMR spectroscopy concludes that the 5-amino-1*H*- isomer dominates, with the 5-amino/3-amino ratio being ca. 2:1 (*22*).

To confirm the structure of *C*-amino-[1,2,4]triazole (amitrole), we synthesized the compound according to ref *11*. This turned out to be identical to the commercially available amitrole (*12*) (based on mps, chromatographic, and spectral characteristics). We recorded its ^1H NMR spectra in $DCON(CD_3)_2$ solution at both low and room temperature. The results (**Table 1**) demonstrated that the 5-amino-1*H*- isomer is predominant.

Studies on the acetylation of 5-amino-1*H*-[1,2,4]triazole (AT) have shown (**Figure 2**) that 1 equiv of acetyl chloride yields an annular N-acetylated product (*23*−*25*). This contains the C═O band at 1732 cm^{-1} in the IR (KBr) spectrum (*23*), and its annular proton chemical shift is 7.57 δ in the ^1H NMR [$(CD_3)_2SO$] spectrum (*25*, *26*), which would indicate the structure of 1-acetyl-5-amino-1*H*-[1,2,4]triazole [AT(Ac); **1**] and not that of 1-acetyl-3-amino-1*H*-[1,2,4]triazole [(AT(Ac′); **2**] as has been incorrectly ascribed (*23*). 1-Acetyl-5-amino-1*H*-[1,2,4]triazole (**1**) in the fused state (*7*, *23*) or in concentrated solutions (*7*) at higher temperatures undergoes an intermolecular (*7*) transacetylation to 5-(acetylamino)-1*H*-[1,2,4]triazole (Ac-AT; **3**). Both monoacetyl isomers **1** and **3**, when treated with the second equivalent of acetyl chloride, are converted to 1-acetyl-3-(acetylamino)-1*H*-[1,2,4]triazole [Ac-AT(Ac′); **4**] (*24*, *25*). The same diacetyl compound was also obtained from 5-amino-1*H*-[1,2,4]triazole with neat acetic anhydride at reflux (*27*). Its hydrolysis furnishes 5-(acetylamino)-1*H*-[1,2,4]triazole (**3**) (*23*, *27*).

Acetyl chloride and acetic anhydride have been reported to give mixtures of acetylated and diacetylated derivatives (but this has never been experimentally documented), which posed a separation problem and led to low isolated yields. Therefore, *N*-acetylimidazole was used for a selective 1-acetyl-5-amino-1*H*-[1,2,4]triazole (**1**) formation (*9*). The reagent is, however, expensive, moisture sensitive, and rather difficult to handle. Furthermore, it was employed in severalfold excess. So far, no contemporary method, with but one exception (*25*), has been used to study the ac(et)ylation reactions of 5-amino-1*H*-[1,2,4]-triazole and to check the homogeneity of the products. Thin-layer chromatography (*9)* lacks sensitivity for showing low percentages of contamination. In this study we reinvestigated the reactions of 5-amino-1*H*-[1,2,4]triazole with acetyl chloride and acetic anhydride using HPLC, GC-MS, ^1H NMR, and FTIR spectroscopy as analytical tools and report our results.

EXPERIMENTAL PROCEDURES

Syntheses of HPLC Standards. *General.* 5-Amino-1*H*-[1,2,4]-triazole, of ∼97% purity, supplied by Fluka, was crystallized from ethanol to give a product of purity ≥99.5% by HPLC. Volatiles from reaction mixtures were removed in vacuo on a rotary evaporator at a bath temperature not exceeding 30 °C. Melting points were determined by differential scanning calorimetry (DSC) using a DSC-2010 calorimeter (Thermal Analysis Instruments) under nitrogen in a closed copper vessel with a heating rate of 10 °C min^{-1}.

1-Acetyl-5-amino-1H-[1,2,4]triazole [AT(Ac); 1]. Acetic anhydride (1.38 mL, 15 mmol) was added to a solution of 5-amino-1*H*-[1,2,4]-triazole (0.84 g, 10 mmol) in dimethylformamide (20 mL). After standing for 1 h at room temperature, the reaction mixture was concentrated and the residue was crystallized from ethanol (10 mL) to give colorless crystals (0.92 g, 73%): mp 158.96 °C [Lit. 91%, 150 °C (*23*); 30%, 151−154 °C (*24*); 60%, 153 °C (*24*); 71%, 148 °C (*7*)]; t_R 5.05, 96.87% purity; ^1H NMR δ 7.540 (s, 1H, N−CH), 7.455 (bs, 2H, NH_2), 2.558 (s, 3H, CH_3) (in accord with ref *7*).

1-Acetyl-3-(acetylamino)-1H-[1,2,4]triazole [Ac-AT(Ac′); 4]. A. A suspension of 5-amino-1*H*-[1,2,4]triazole (1.26 g, 15 mmol) in acetic anhydride (15 mL) was stirred for 20 h, the reaction mixture evaporated, and the residue crystallized from acetonitrile (4 mL) to give colorless crystals (1.28 g, 51%): mp 195.91 °C [Lit. 190−191 °C (*27*); 38%, 191−193 °C (*24*); 48%, 190 °C (*24*)]; t_R 6.21, 92.00% purity; ^1H NMR δ 10.760 (s, 1H, NH), 9.108 (s, 1H, N−CH) (*25*, *26*), 2.582 (s, 3H, CH_3-ring), 2.073 (s, 3H, CH_3).

B. A suspension of 5-amino-1*H*-[1,2,4]triazole (0.84 g, 10 mmol) in acetic anhydride (50 mL) was stirred for 6 days, and the reaction

Table 2. Chemical Shifts of 5-(Acetylamino)-1*H*-[1,2,4]triazole (**3**) in $DCON(CD_3)_2$

Compound	Temp. °C	Chemical shifts (ppm) bs, NH-ring	s, CO-NH	s, N-CH
 Major set		13.894	11.953	7.705
	-50			
 Minor set		14.159[a]		8.521[a]
	20	13.326	11.507	7.674
				8.313[a]

[a] Without integral.

mixture was evaporated to furnish colorless crystals (1.68 g, 100%): mp 195.65 °C; t_R 6.21, 96.45% purity.

5-(Acetylamino)-1H-[1,2,4]triazole [(Ac-AT); 3]. A solution of 5-amino-1*H*-[1,2,4]triazole (0.84 g, 10 mmol) in acetic anhydride (25 mL) was refluxed for 1 h and evaporated. Water (50 mL) was added to the residue, and the suspension was stirred for 24 h. The precipitate was filtered off to give colorless crystals (1.12 g, 89%): mp 298.94 °C [Lit. 295−300 °C (*27*); 100%, 288 °C (*23*); 95%, 287−288 °C (*23*)]; t_R 2.82, 100.00% purity; ^{1}H NMR δ 13.283 (s, 1H, NH-ring), 11.105 (s, 1H, CONH), 7.841 (s, 1H, N−CH) (*25*, *26*), 2.073 (s, 3H, CH_3). Evidence for the tautomeric proton position of the compound is given in **Table 2**.

HPLC. The results of acetylation experiments were followed using a Beckman chromatographic system. It consisted of a model 126 programmable module, a model 168 diode array detector, and a model 210A injection valve. The separations were performed on an Alltech Alltima, C_{18}, 5 μm, 150 × 4.6 mm reversed-phase column with a 5 μL injection loop. The mobile phase was 0.1% trifluoroacetic acid/ACN (95:5) at a flow rate of 1 mL min^{-1}. Detection was made at 210 nm as a rule and at 250 nm in some instances.

^{1}H NMR. Spectra were acquired in $DCON(CD_3)_2$ solution (**Tables 1** and **2**) or in $(CD_3)_2SO$ solution (**Table 3** and **Figure 3**) on a Bruker Advance DRX 300 MHz instrument, with tetramethylsilane as internal standard.

FTIR. Spectra were recorded on a Philips Analytical PU9800 FTIR spectrometer at 2 cm^{-1} nominal resolution in KBr and Nujol.

GC-MS. An HP 6890 gas chromatograph with an HP-5 column and an MS 5973 (EI) mass spectrometer as detector were used.

RESULTS AND DISCUSSION

Two detailed procedures for preparing 1-acetyl-5-amino-1*H*-[1,2,4]triazole [AT(Ac); **1**] from 5-amino-1*H*-[1,2,4]triazole using 1 equiv of acetyl chloride have been described (**Figure 2**); both were carried out in suspension either (i) in tetrahydrofuran at 20 °C (20 h, 91% isolated yield; *23*) or (ii) in acetonitrile at 65−70 °C (1.5 h, 30% isolated yield; *24*). HPLC examination shows slow progress of the former reaction and reveals that both yield a mixture of two isomeric monoacetyl derivatives, 1-acetyl-5-amino-1*H*-[1,2,4]triazole [AT(Ac); **1**] and 5-(acetylamino)-1*H*-[1,2,4]triazole (Ac-AT; **3**), in a 10:1 ratio in the former and in a 2.5:1 ratio in the latter procedure (**Table 3**, A and B). We did not find the diacetyl derivative, as suggested by others (*9*). The outcome of the latter procedure and its low isolated yield of the major product are not a surprise as the reaction proceeds on heating. However, a tetrahydrofuran solution of 1-acetyl-5-amino-1*H*-[1,2,4]triazole (**1**) left standing at 20 °C under the conditions of reaction i displays a <1% increase in Ac-AT (**3**) amount. Thus, the isomeric compound Ac-AT (**3**) in the former procedure was formed by direct acetyl chloride action rather than by the transacetylation pathway.

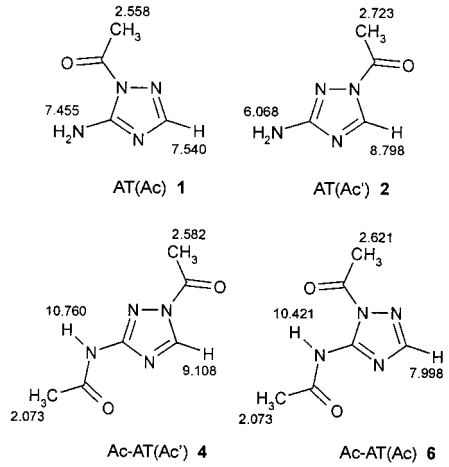

Figure 3. Proton chemical shifts (ppm) of acetylated *C*-amino-[1,2,4]-triazoles in a $(CD_3)_2SO$ solution (units have been omitted for clarity).

We tried a milder acetylating agent in a 5-amino-1*H*-[1,2,4]-triazole-solubilizing medium. The substrate, treated with 1 equiv of acetic anhydride in dimethylformamide at 20 °C, disappeared almost completely after 30 s to furnish, as expected, the desired AT(Ac) (**1**) in an acceptable ratio to Ac-AT (**3**) (**Table 3**, C). However, we unexpectedly found the third isomer, 1-acetyl-3-amino-1*H*-[1,2,4]triazole, AT(Ac′) (**2**), in the postreaction mixture. The ratio of AT(Ac) (**1**) to AT(Ac′) (**2**) was 9:1. AT(Ac′) (**2**) has been postulated (*28*) as the intermediate in the

Table 3. Acetylation Experiments on 5-Amino-1*H*-[1,2,4]triazole (A–I[a]), 1-Acetyl-5-amino-1*H*-[1,2,4]triazole (**1**) (J), and 5-(Acetylamino)-1*H*-[1,2,4]triazole (**3**) (K)[b]

		1 equiv of acetylating agent						excess acetylating agent								
compound	t_R[c] (min)	A (%)	B (%)	C (%)	C′ (%)	C″ (%)	D (%)	E (%)	F (%)	G (%)	G′ (%)	H (%)	I (%)	J (%)	J′ (%)	K (%)
AT	2.06	2.0	10.4	1.3	3.2	7.7				0.6	0.3		3.9			
AT(Ac) **1**	5.05	87.2	63.1	85.3	90.0	68.5	58.4			7.0			60.6	3.2		
Ac-AT **3**	2.82	8.5	23.4	1.3	5.5	23.8	7.4	8.1	2.0	12.6	9.7	4.1	9.6	5.3	25.9	5.4
AT(Ac′) **2**	4.23			9.6	0.6		23.2									
Ac-AT(Ac′) **4**	6.21							74.9	41.1	73.0	90.0	95.4	6.6	55.7	56.2	94.6
Ac-AT(Ac) **6**	9.84									6.2			17.2	35.7	17.9	
Ac_2=AT(Ac*)[d] **5**	28.8							6.1	39.6							
Σ others[e]		2.3	3.1	2.5	0.7		11.0	10.9	17.3	0.6		0.5	2.1	0.1		

[a] Data A–I for 1 equiv of AT; A, according to ref *23*, additional equiv of AT, 1 equiv of Ac-Cl, 10 mL of THF, 20 °C, 20 h; B, according to ref *24*, 1 equiv of *s*-collidine, 1 equiv of Ac-Cl, 1.5 mL of ACN, 65–70 °C, 1.5 h; C, 1 equiv of Ac_2O, 0.33 mL of $HCON(CH_3)_2$, 20 °C, 0.5 min; C′, postexperiment C residue after 1 month; C″, postexperiment C residue after 3 months; D, 1 equiv of Ac_2O, 1 mL of $(CH_3)_2SO$, 20 °C, 2 min; E, according to ref *27*, 7.5 equiv of Ac_2O, reflux, 5 min; F, 53 equiv of Ac_2O, reflux, 2 h; G, 13 equiv of Ac_2O, 20 °C, 20 h; G′, 13 equiv of Ac_2O, 20 °C, 7 days; H, 53 equiv of Ac_2O, 20 °C, 6 days; I, 10 equiv of Ac_2O, 2.0 mL of $HCON(CH_3)_2$, 20 h; J, 1 equiv of AT(Ac) (**1**), 53 equiv of Ac_2O, 20 °C, 48 h; J′, postexperiment J residue after 3 days; K, 1 equiv of Ac-AT (**3**), 53 equiv of Ac_2O, 20 °C, 48 h. [b] Composition of crude postreaction mixtures by HPLC (idenitification of products by ^{1}H NMR, FTIR, and MS). [c] Retention time. [d] * denotes uncertain position of the ring Ac. [e] Unidentified.

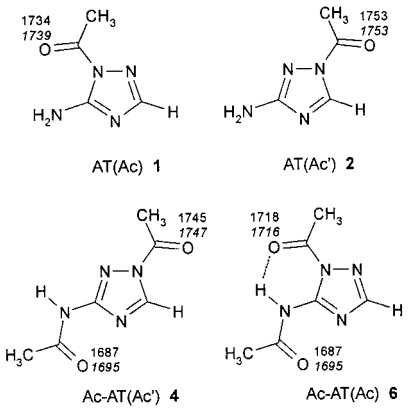

Figure 4. Frequencies in the AI region (cm^{-1}) of acetylated *C*-amino-[1,2,4]triazoles in KBr and Nujol (units have been omitted for clarity).

ring acetylation of 5-amino-1*H*-[1,2,4]triazole but has never been observed previously (*7*). Given the latter compound, the ratio of the annular isomers [AT(Ac) + AT(Ac′); **1** + **2**] to the acetamido isomer, Ac-AT (**3**), was 73:1. AT(Ac′) (**2**) was also detected, to an even larger extent, AT(Ac) (**1**) to AT(Ac′) (**2**) in an approximately 2.5:1 ratio, when 5-amino-1*H*-[1,2,4]triazole reacted with 1 equiv of acetic anhydride in dimethyl sulfoxide (**Table 3**, D). Analogous intermediates, although not yet identified in the reactions with the usual acyl agents, were recognized with alkoxycarbonyl chlorides, and the nature of solvent had a substantial effect on the annular isomer ratio (*7*, *8*, *29*).

The annular isomer mixture of AT(Ac) and AT(Ac′) (**1** + **2**) (expt D) shows two ^{1}H NMR signal sets (**Figure 3**). The predominant signals, 7.540, 7.455, and 2.558 ppm, belong to the N−CH, NH_2, and CH_3 protons of 1-acetyl-5-amino-1*H*-[1,2,4]triazole [AT(Ac); **1**], respectively (*7*, *25*, *26*, *29*, *30*). The other, a minor set at 8.798, 6.068, and 2.723 ppm, may be ascribed in sequence to the N−CH, NH_2, and CH_3 protons of 1-acetyl-3-amino-1*H*-[1,2,4]triazole [AT(Ac′); **2**]. As predicted, the N−CH proton of the latter compound is characteristically deshielded (*25*, *26*) by the acetyl group and the NH_2 protons become, in turn, shielded by the lone electron pair (*29*). The above assignments closely resemble those for the couples of the corresponding annular alkoxycarbonyl isomers resulting from the reaction of 5-amino-1*H*-[1,2,4]triazole with alkyl chlorocarbonates (*7*, *29*) (e.g., diagnostic values are 7.52 and 7.31 ppm for the 5-amino-1-ethoxycarbonyl isomer and 8.69 and 6.00 ppm for the 3-amino-1-ethoxycarbonyl isomer; *29*).

The FTIR spectrum (KBr) of the mixture from expt C provides corroborative evidence of the existence of AT(Ac′) (**2**). It displays in the AI region a strong band at 1734 cm^{-1}, characteristic of the C═O group of AT(Ac) (**1**) (1732 cm^{-1}; *23*), and a weak band at 1753 cm^{-1}, which may be ascribed to the C═O group of AT(Ac′) (**2**) (**Figure 4**). In the Nujol mull spectrum, both bands, positioned at 1739 and 1753 cm^{-1}, respectively, are equal in intensity. When this Nujol mull sample was left standing for half an hour, the spectrum in the discussed region exhibits only the band at 1753 cm^{-1}. When we started the measurements with pure AT(Ac) (**1**) in the Nujol mull, the initial band at 1739 cm^{-1} also passed into the band at 1753 cm^{-1}. Frequency 1753 cm^{-1} compares well to the literature IR data (in KBr) obtained for cognate molecules. The vibrational frequencies 1757 and 1745 cm^{-1} are due to the carbonyl of 1-acetyl-1*H*-[1,2,4]triazole itself (*23*) and the annular carbonyl of 1-acetyl-3-(acetylamino)-1*H*-[1,2,4]triazole (**4**) (*23*), respectively. The C═O group frequencies for a couple of annular alkoxycarbonyl isomers are at 1740 cm^{-1} for the 5-amino isomer and at 1770 cm^{-1} for the 3-amino isomer (*29*).

The AT(Ac′) isomer **2** is not stable. The postexperiment C solution after 20 h of standing displays only half its starting amount of AT(Ac′) (**2**). This solution was evaporated and the residue then stored at 20 °C for 1 month. It showed a further decrease in AT(Ac′) (**2**) and increases in AT(Ac) (**1**) and Ac-AT (**3**) amounts (**Table 3**, C′). After an additional 2 months of storage, the sample no longer contained AT(Ac′) (**2**) at all and showed much more Ac-AT (**3**) at the expense of AT(Ac) (**1**). The ratio of Ac-AT (**3**) to AT(Ac) (**1**) increased to approximately 1:2.9 (**Table 3**, C″) and remained almost unchanged even after a further 6 months of storage. With the pure, solid-state AT(Ac) isomer **1**, about the same ratio was reached after 3 months. The crystallization of the postexperiment C mixture from ethanol removed some unidentified compounds and some fraction of Ac-AT (**3**) but did not cause any significant change in the ratio of AT(Ac) (**1**) to AT(Ac′) (**2**), as they proved to be similar in solubility. In the crystallized sample, the rearrangement of AT(Ac′) (**2**) into AT(Ac) (**1**) is much slower than that in the crude state; the amount of AT(Ac′) (**2**) decreased from 11.1 to 9.0% after 1 month of storage. The crystallized sample, when left standing in distilled water at neutral pH for 20 min, did not hydrolyze but did in water at pH 2.0. About half of the AT(Ac′) (**2**) disappeared, whereas only 25% of the AT(Ac) (**1**) was hydrolyzed. Therefore, the intermediate **2** of the 5-amino-1*H*-[1,2,4]triazole annular monoacetylation was more susceptible to hydrolysis than the final product **1**.

Ac-AT(Ac′) (**4**) was prepared first of all in a one-pot diacetylation of 5-amino-1*H*-[1,2,4]triazole by boiling for 5 min with neat acetic anhydride. No yields were given (*27*). HPLC and GC-MS analysis of a crude postreaction mixture, provided by this protocol, indicated 1-acetyl-3-(acetylamino)-1*H*-[1,2,4]-triazole (**4**) to be the major product and additionally a mono (M^+ 126) and a triacetyl derivative (M^+ 211). These byproducts are 5-(acetylamino)-1*H*-[1,2,4]triazole (**3**) and 1-acetyl-*x*-(bisacetyl)amino-1*H*-[1,2,4]triazole (**5**), most likely 1-acetyl-3-(bisacetyl)amino-1*H*-[1,2,4]triazole (**Table 3**, E). Longer heating in a large excess of anhydride significantly increased the amount of the latter (**Table 3**, F). Hence, we tried to synthesize Ac-AT(Ac′) (**4**) at 20 °C. Under these conditions, 5-amino-*1H*-[1,2,4]triazole does not dissolve in neat acetic anhydride. However, the reaction mixture contained 73% of the diacetyl derivative Ac-AT(Ac′) (**4**) and no triacetyl derivative after 20 h (**Table 3**, G). Evaporation and crystallization yields 51% of Ac-AT(Ac′) (**4**). If the crude reaction mixture from expt G was further stirred for up to 7 days, the amount of Ac-AT(Ac′) (**4**) grew to 90% (**Table 3**, G′). To get a better preparative result, one could force the reaction yield to ∼95% of Ac-AT(Ac′) (**4**) by using a 50-fold molar amount of acetic anhydride and leaving the reacting suspension for 6 days (**Table 3**, H).

In an effort to perform the diacetylation in solution instead of suspension in neat acetic anhydride, we tried dimethylformamide, being encouraged by the instantaneous acetylation of the ring nitrogen atom with 1 equiv of anhydride in this solvent (cf. **Table 3**, C). In a dimethylformamide solution, acetic anhydride in 10-fold molar amount, after 20 h gave largely the 1-acetyl-5-amino derivative **1**, only a small amount of Ac-AT-(Ac′) (**4**), and, unexpectedly, similarly to the process of 1 equiv acetylation in this medium, an atypical product of diacetylation, Ac-AT(Ac) (**6**) (**Table 3**, I). Therefore, it seems then that dimethylformamide does not favor acetic anhydride exoacetylation of 5-amino-1*H*-[1,2,4]triazole. This solvent has previously been marginally mentioned to be less appropriate com-

pared to tetrahydrofuran for a global acylation of 5-amino-1*H*-[1,2,4]triazole (*4*). To make apparent the atypical product of diacetylation, we started with AT(Ac) (**1**) and acylated it with acetic anhydride in a large excess, at 20 °C for a short time (**Table 3**, J). As expected, we obtained a mixture with a large content of Ac-AT(Ac) (**6**). Comparison of the result of expt G [73% of Ac-AT(Ac′) (**4**) after 20 h] with that of expt J [55% of Ac-AT(Ac′) (**4**) after 48 h] shows that direct exoacetylation of AT(Ac′) (**2**) contributed to the results of the former experiment. The results of expt G and J are also in line with the result of expt K, in which we started with 5-(acetylamino)-1*H*-[1,2,4]-triazole (**3**). The substrate in neat acetic anhydride undergoes acetylation to 1-acetyl-3-(acetylamino)-1*H*-[1,2,4]triazole (**4**), but the formation of 1-acetyl-5-(acetylamino)-[1,2,4]triazole (**6**) could not be observed in this reaction.

The annular isomer mixture of diacetyl derivatives, that is, Ac-AT(Ac′) (**4**) and Ac-AT(Ac) (**6**) (expt J), shows two ^{1}H NMR signal sets (**Figure 3**). The predominant set, 10.760, 9.108 (*25*, *26*), 2.582, and 2.073 ppm, may be ascribed, respectively, to the CONH, N−CH, CH_3CO ring, and CH_3 acetamido protons of 1-acetyl-3-(acetylamino)-1*H*-[1,2,4]triazole [Ac-AT(Ac′); **4**]. The other, the minor set 10.421, 7.998, 2.621, and 2.073 ppm, may be assigned in sequence to the CONH, N−CH, CH_3CO ring, and CH_3 acetamido protons of 1-acetyl-5-(acetylamino)-1*H*-[1,2,4]triazole [Ac-AT(Ac); **6**]. In the latter set, the N−CH proton is characteristically shielded by the lone electron pair (*25*, *26*, *29*). The presence of Ac-AT(Ac) (**6**) is confirmed by FTIR spectroscopy. The FTIR spectrum of a mixture of Ac-AT(Ac′) (**4**) and Ac-AT(Ac) (**6**) in KBr displays in the AI region three C═O bands (**Figure 4**): (i) the band at 1745 cm^{-1} characteristic of the annular acetyl group of the known Ac-AT(Ac′) (**4**) (1745 cm^{-1}, KBr; *23*); (ii) the band at 1687 cm^{-1} characteristic of the acetamido C═O group [1689 cm^{-1}, KBr; for Ac-AT (**3**), *23*]; and (iii) a band at 1718 cm^{-1}. This last one, which is red-shifted by 16 cm^{-1} with respect to the free carbonyl group of AT(Ac) (**1**) (1734 cm^{-1}), is ascribable to the C═O group of the hitherto unknown Ac-AT(Ac) (**6**), involved in hydrogen bonding with the contiguous acetamido group. The hydrogen bond, however, was not observed in the NMR spectrum taken in a $(CD_3)_2SO$ solution (cf. **Figure 3**). The mixture of Ac-AT(Ac′) (**4**) and Ac-AT(Ac) (**6**) in Nujol mull shows also three bands positioned similarly (1747, 1695, and 1716 cm^{-1}) as those in KBr. In strong contrast to a mixture of the annular monoacetyl isomers, here, no migration of the annular acetyl groups occurs.

The evaporated postexperiment J mixture was left to stand for 3 days and showed (expt J′) half its starting amount of Ac-AT(Ac) (**6**) and an increase in Ac-AT (**3**), whereas the content of Ac-AT(Ac′) (**4**) remained constant. The rates of hydrolysis of both isomers in both pure water and water at pH 2 were comparable. The above changes of the postexperiment J mixture content points then to the existence of a mechanism of annular deacetylation of Ac-AT(Ac) (e.g., under the influence of some residual acetic acid).

CONCLUSION

The results obtained suggest the main stepwise pathways for the acetylation of 5-amino-1*H*-[1,2,4]triazole with acetic anhydride at room temperature (**Figure 5**). These may be accompanied by transacetylation from an *N*-annular position to the exocyclic amino group (*7*, *23*). The knowledge gained may be useful for developing effective and selective preparative procedures for the acetylation of 5-amino-1*H*-[1,2,4]-triazole. It remains to be elucidated whether the transacetylation between the annular positions, as shown in **Figure 5**, is an intermolecular or an intramolecular process.

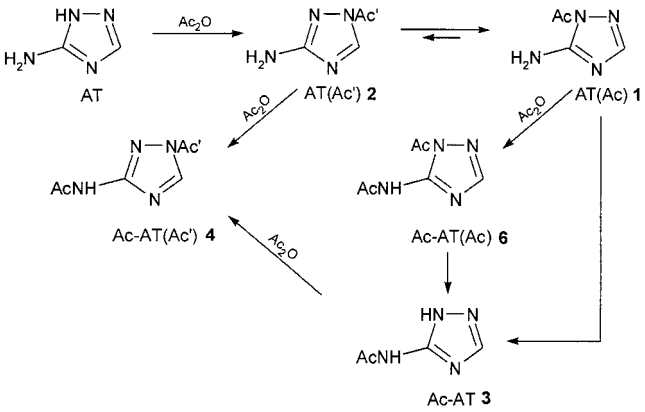

Figure 5. Hypothetical pattern for the acetylation of 5-amino-1*H*-[1,2,4]-triazole with Ac_2O at room temperature.

ABBREVIATIONS USED

HPLC, high-performance liquid chromatography; GC-MS, gas chromatography−mass spectrometry; ^{1}H NMR and ^{13}C NMR, proton and carbon magnetic resonance, respectively; FTIR, Fourier transform infrared spectroscopy; AT, 5-amino-1*H*-[1,2,4]triazole; Ac, acetyl; AT(Ac), 1-acetyl-5-amino-1*H*-[1,2,4]triazole; AT(Ac′), 1-acetyl-3-amino-1*H*-[1,2,4]triazole; Ac-AT, 5-(acetylamino)-1*H*-[1,2,4]triazole; Ac-AT(Ac′), 1-acetyl-3-(acetylamino)-1*H*-[1,2,4]triazole; Ac-AT(Ac), 1-acetyl-5-(acetylamino)-1*H*-[1,2,4]triazole; Ac_2=AT(Ac′), 1-acetyl-*x*-(bisacetyl)amino-1*H*-[1,2,4]triazole; ACN, acetonitrile; THF, tetrahydrofuran.

ACKNOWLEDGMENT

We express our gratitude to Professor Paweł Kafarski for providing the access to NMR spectrometers and to Tomasz Cierpicki for recording these spectra.

LITERATURE CITED

(1) Boyer, J. H. Monocyclic Triazoles and Benzotriazoles. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; Wiley: New York, 1961; Vol. 7, pp 460−461.
(2) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Georg Thieme Verlag: Stuttgart, Germany, 1995; p 211.
(3) Hutson, D. H.; Lee, P. W.; Nicholls, P. H.; Plimmer, J. R. Triazoles. Amitrole. In *Metabolic Pathways of Agrochemicals*, Part 1; Roberts, T. M., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1998; pp 671−677.
(4) Hartmann, M.; Saupe, S.; Wermann, K. Biocide Polymere; Chemische Fixirung des Herbicids 3-Amino-1*H*-1,2,4-triazol an Maleisäureanhydrid-Copolymere. *Z. Chem.* **1987**, *27*, 139−140.
(5) Wermann, K.; Stein, S.; Moszner, N. Hydrolytische Freisetzung des Herbicids 3-Amino-1*H*-1,2,4-triazol aus modifizierten Maleinsäureanhydrid-Copolymere. *Z. Chem.* **1987**, *27*, 439−440.
(6) Potts, K. T.; Crawford, T. H. Structures of *N*-Acyl-*s*-triazoles. *J. Org. Chem.* **1962**, *27*, 2631−2632.
(7) Fidler, Zh. N.; Shibanova, E. F.; Makerov, P. V.; Kalikhman, I. D.; Shulunova, A. M.; Sarapulova, G. I.; Klyba, L. V.; Vitkovskii, V. Yu.; Chipanina, N. N.; Lopyrev, V. A.; Voronkov, M. G. Acyl Derivatives of 3-Amino-1,2,4-triazole. *Chem. Heterocycl. Compd.* (*Engl. Trans.*) **1980**, 1079−1083.
(8) Winkler, T.; Kristinsson H. Die Acylierung von 5-Amino-1*H*-1,2,4-triazolen. Eine ^{13}C-NMR-Studie. *Helv. Chim. Acta* **1983**, *66*, 694−700.

(9) Look, M.; White, L. R. Synthesis of 2-Acyl-3-amino-1,2,4-triazoles and 2-Acetyl-3-amino-1,2,4-triazole-5-^{14}C. *J. Agric. Food Chem*. **1972**, *20*, 824−825.
(10) In *Beilstein Handbuch der Organische Chemie* (a) *26*, 137; I, 38; II, 76; (b) III/IV, 1073.
(11) Sjostedt, G.; Gringas, L. 3-Amino-1*H*-1,2,4-triazole In *Organic Syntheses*; Horning, E. C., Ed.; Wiley: London, U.K., 1964; Collect. Vol. 3, pp 95−96.
(12) *Lancaster 1997−1999 Katalog*, p 107.
(13) Makarskii, V. V.; Zubkov, B. A.; Lopyrev, V. A.; Voroknov, M. G. Kvantovochimiczeskii Analiz Tautomerii 1,2,4-Triazola i jego Amino- i Diaminoproizvodnych. *Khim. Geterosikl. Soedin.* **1977**, 540−545; *Chem. Abstr*. **1977**, *87*, 67696w.
(14) Parchment, O. W.; Hillier, I. H.; Green, D. V. S.; Burton, N. A.; Morley, J. O.; Schaefer, H. F., III A Theoretical Study, using *ab initio* Methods, of Tautomerism in 3-Amino-1,2,4-Triazole in the Gas Phase and in Aqueous Solution. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1681−1684.
(15) Makarskii, V. V.; Starova, G. L.; Frank-Kamenetskaya, O. V.; Lopyrev, V. A.; Voronkov, M. G. Molekulyarnaya Struktura 3-Amino-1,2,4-triazola. *Khim. Geterosikl. Soedin.* **1977**, 1138−1139; *Chem. Abstr.* **1977**, *87*, 167950t.
(16) Starova, G. L.; Frank-Kamenetskaya, O. V.; Makarskii, V. V.; Lopyrev, V. A. Kristalliczeskaya i Molekulyarnaya Struktura 5-Amino-1-vodorod-1,2,4-triazola. *Krystallografiya* **1978**, *23*, 849−851; *Chem. Abstr*. **1978**, *89*, 179339e.
(17) Jia-Rong, L.; Bo-Ren, Ch.; Yu-Xiang, O.; Xiu-Shan, C.; Zuo-Cai, L. Structure of the 3-Amino-1,2,4-triazolium Salt of 3-Nitro-1,2,4-triazol-5-one. *Acta Crystallogr*. **1992**, *C48*, 1540−1542.
(18) Lynch, D. E.; Smith, G.; Byriel, K. A.; Kennard, C. H. L. Molecular Cocrystals of Carboxylic Acids. 8. Structure of the 1:1 Adduct of 3,5-Dinitrobenzoic Acid with 3-Amino-1*H*-1,2,4-triazole. *Acta Crystallogr*. **1992**, *C48*, 1265−1267.
(19) Byriel, K. A.; Kennard, C. H. L.; Lynch, D. E.; Smith, G.; Thompson, J. G. Molecular Cocrystals of Carboxylic Acids. IX. Carboxylic Acid Interactions with Organic Heterocyclic Bases. The Crystal Structures of the Adducts of (2,4-Dichlorophenoxy)-acetic Acid with 3-Hydroxypyridine, 2,4,6-Trinitrobenzoic Acid with 2-Aminopyrimidine, and 4-Nitrobenzoic Acid with 3-Amino-1,2,4-triazole. *Aust. J. Chem.* **1992**, *45*, 969−981.
(20) Lynch, D. E.; Smith, G.; Byriel, K. A.; Kennard, C. H. L. Molecular Cocrystals of Carboxylic Acids. 16. 1:1 Adduct of 3-Nitrobenzoic Acid with 3-Amino-1*H*-1,2,4-triazole. *Acta Crystallogr*. **1994**, *C50*, 1291−1294.
(21) Butler, R. N.; McEvoy, T.; Alcalde, E.; Claramunt, R. M.; Elguero, J. Aromatic Systems with 10π Electrons Derived from 3a-Azapentalene. Part 37. Cyclization of the Anion of Azido-*s*-triazole into the Anion of *s*-Triazolo[2,3-*d*]tetrazole. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2886−2890.
(22) Fritz, H. Nitrogen-15 NMR Spectroscopy−Application in Heterocyclic Chemistry. *Bull. Soc. Chim. Belg.* **1984**, *93*, 559−569.
(23) Staab, H. A.; Seel, G. Über *N*-Acyl-Derivative des 3-Amino-1.2.4-triazols. *Chem. Ber*. **1959**, *92*, 1302−1306.
(24) Van den Bos, B. G. Investigations on Pesticidal Phosphorus Compounds II. On the Structure of Phosphorus Compounds Derived from 3-Amino-1,2,4-triazole. *Recl. Trav. Chim*. **1960**, *79*, 836−842.
(25) Coburn, M. D.; Loughran, E. D.; Smith, L. C. The Acetylation of 3-Amino-1,2,4-triazole. *J. Heterocycl. Chem.* **1970**, *7*, 1149−1151.
(26) Coburn, M. D.; Jackson, T. E. Picrylamino-substituted Heterocycles. III. 1,2,4-Triazoles. *J. Heterocycl. Chem*. **1968**, *5*, 199−203.
(27) Birkofer, L. Über Diacylderivative primärer heterocyclischer Amine. *Chem. Ber*. **1943**, *76*, 769−773.
(28) Sainsbury, M. Five-Membered Heterocyclic Compounds with Three Hetero-Atoms in the Ring. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Ansell, M. F., Ed.; Elsevier: Amsterdam, The Netherlands, 1986; Vol. 4, Part D (Heterocyclic Compounds), p 50.
(29) Hirata, T.; Wood, H. B.; Driscoll, J. S. Rearrangement and Elimination Reactions of 1,2,4-Triazole Derivatives. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1209−1212.
(30) Reiter, J. On Triazoles. XXXIV. The Correct Structure of the Ethoxycarboxylated 5-Amino-1*H*-1,2,4-triazole and its Product with Hydrazine. *J. Heterocycl. Chem*. **1994**, *31*, 745−748.

Received for review June 4, 2001. Revised manuscript received December 16, 2001. Accepted December 17, 2001. We express our gratitude to The Polish State Committee for Scientific Research (KBN) for the financial support.

JF010734A