Pyrazolo[1,5-*a*]pyrimidine: Synthesis and Regiospecific Electrophilic Substitution in the Pyrazole and/or Pyrimidine Rings[1]

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A general cyclization route to pyrazolo[1,5-*a*]pyrimidines from 3-aminopyrazole and 1,3-dicarbonyl compounds is applied to synthesis of the parent ring system. In nitration of this species the orientation of substitution is strongly reagent dependent. Mixed nitric and sulfuric acids yield the 3-nitro compound, whereas nitric acid in acetic anhydride yields the 6-nitro compound. Brominations yield 3-bromo and 3,6-dibromo species.

The majority reacting species in the strongly acidic medium is identified as the 1-protonated entity by conjoint use of approximate molecular orbital calculations and the variation of coupling constant patterns accompanying protonation. The molecular orbital calculations predict successive 3- and 6-substitution by electrophiles in pyrazolo[1,5-*a*]pyrimidine and its conjugate acid, and an addition–elimination sequence is proposed to account for the observed 6-nitration.

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Une méthode générale de cyclisation conduisant aux pyrazolo[1,5-*a*]pyrimidines, à partir des amino-3 pyrazole et des composés dicarbonylés 1,3, est appliquée à la synthèse de ces systèmes cycliques fondamentaux. Lors de la nitration de ces espèces, l'orientation de la substitution dépend beaucoup de la nature du réactif. Un mélange d'acides nitrique et sulfurique conduit au composé portant un groupe nitro en position 3 alors que l'acide nitrique dans l'anhydride acétique conduit au composé portant un groupe nitro en position 6. La bromuration conduit aux dérivés bromo-3 et dibromo-3,6.

On a identifié les espèces réagissant d'une façon prédominante dans les milieux fortement acide comme étant les entités protonées en position 1; cette conclusion a été établie par l'utilisation à la fois de calcul d'orbitales moléculaires approché et la variation de patron de constante de couplage accompagnant la protonation. Les calculs d'orbitales moléculaires prédisent des substitutions électrophiles successives en position 3 et 6 pour les pyrazolo [1,5-*a*]pyrimidines et leurs acides conjugués et l'on propose une séquence d'addition et d'élimination pour tenir compte de la nitration observée en position 6. [Traduit par le journal]

Introduction

As part of a systematic synthesis program for fused-ring species derived from pyrazole (1, 2), we communicated in 1970 (1) a brief account of routes to pyrazolo[1,5-*a*]pyrimidine **1** and some 3-substituted derivatives. Patent claims to a similar synthetic route (3) and reports of enzyme-inhibitory activity for 3-substituted 5,7-dimethylpyrazolo[1,5-*a*]pyrimidines (4 and references therein) prompt us to provide details of the synthesis of **1**, and to report and analyze the patterns revealed in its common electrophilic substitutions and in its p.m.r. spectra, using an interpretive framework of π-electron (HMO) and all-valence-electron (CNDO/2) quantum chemical calculations.

Results

The parent species **1** is available in excellent yield by a sequential condensation and electrophilic cyclization, employing 1,1,3,3-tetramethoxypropane (malondialdehyde tetramethylacetal) and 3-aminopyrazole (generated by thermal decarboxylation of the commercially available 3-aminopyrazole-4-carboxylic acid) with zinc chloride in refluxing ethanolic solution. This route is based on related precedents in the Russian literature (5) and we have also applied

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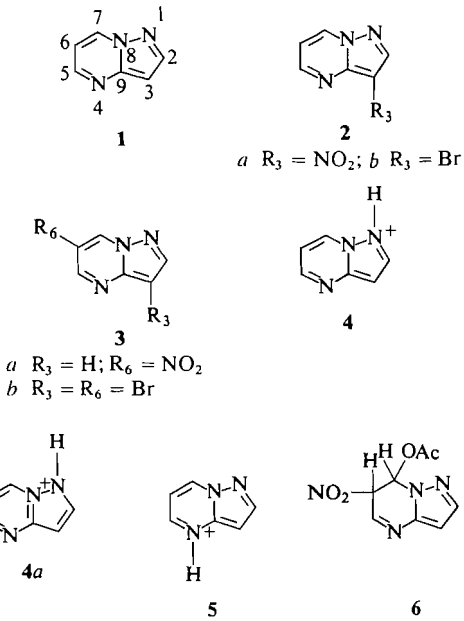
it to construction of compounds in the isomeric pyrazolo[3,4-*b*]pyridine series (1, 6).

One of our purposes in examining the patterns of electrophilic substitution of **1** was to seek further examples of *reagent-dependent orientation* (as explored previously for brominations and nitrations of arylpyrazoles (7, 8), acetanilides (9), and arylpyrimidines (10)). In considering such substitutions, the actual reacting species could be either the free base **1** or a conjugate acid species, and the favored positions of substitution might differ for attack on each entity. The expectation of reagent-dependent orientation was fulfilled for nitration reactions: treatment of **1** with mixed concentrated nitric and sulfuric acids at 0 ± 5° (standard conditions for mononitration of arylpyrazoles (7, 8)) gave the 3-nitropyrazolo[1,5-*a*]pyrimidine **2***a*, whereas corresponding treatment with nitric acid – acetic anhydride gave the 6-nitropyrazolo-[1,5-*a*]pyrimidine **3***a*, with each reaction being regiospecific.

In contrast, brominations under a variety of conditions (6) provided the 3-bromopyrazolo-[1,5-*a*]pyrimidine **2***b* and/or 3,6-dibromopyrazolo[1,5-*a*]pyrimidine **3***b* but there was no indication of initial 6-substitution.

The formation of **2***a* in nitration of **1** corresponds to the orientation in mononitration of pyrazolo[1,5-*a*]pyridine (2), whereas the 6-nitration to **3***a* has precedent in the nitration of tetrazolo[1,5-*a*]pyridine (11).



Discussion

Explanation of the Regioselective Nitrations

The remarkable feature of the nitration results is that their sense is opposite to that observed in the nitrations of arylpyrazoles (7, 8) and pyrazolo[1,5-*a*]pyridine (2), where we found that the nitric acid – acetic anhydride reagent favors attack in the pyrazole moiety. A necessary starting point for an explanation is a definition of the majority reacting species in the nitration media. The pK_a of the conjugate acid derived from **1** is 2.30 (determined potentiometrically (6)), suggesting very strongly that the majority species in the mixed acid nitrations of **1** will be this conjugate acid (compare pyrazole and 1-arylpyrazoles, of similar basic strength to **1**, where kinetic proof of nitration via the conjugate acid species has been given (12, 13).

The species **1** could undergo either 1-protonation (to entity **4**) or 4-protonation (to entity **5**) and it is difficult to decide between these potential basic centers (the 1- or the 4-nitrogen). The results of quantum-chemical calculations favor **4**: thus the π-electron distribution from a HMO calculation on **1** (Fig. 1) indicates that position 1 would be protonated first (accepting that a proton would attach itself most readily to the nitrogen atom of highest π-electron density (*cf.* 14), and HMO calculations of the π-electron binding energies of assumed models of **4** and **5** (which give respective values of 13.353 and 13.297 β) indicate that **4** is the more stable entity. The all-valence-

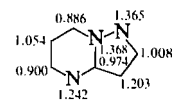


FIG. 1. HMO π-electron densities for species **1**

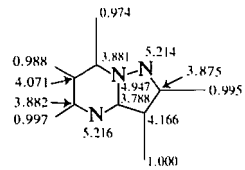


FIG. 2. CNDO/2 electron densities for species **1**.

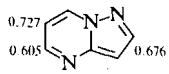


FIG. 3. HMO π-bond orders for species **1**.

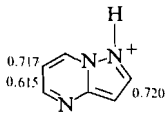


FIG. 4. HMO π-bond orders for species **4**.

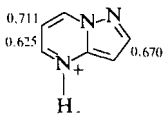


FIG. 5. HMO π-bond orders for species **5**.

electron CNDO/2 calculation for **1** (Fig. 2) yields virtually identical total electron densities (5.214 at nitrogen-1, 5.216 at nitrogen-4) but the 2s electron populations (corresponding to the lone-pair basic center) strongly favor protonation at nitrogen-1 (the 2s electron populations are 1-nitrogen, 1.520; 4-nitrogen, 1.458).

Furthermore, conjoint comparison of the calculated HMO π-bond orders for **1**, **4**, and **5** (see Figs. 3–5) with changes in the magnitudes of interproton couplings accompanying protonation of **1** (as revealed by the comparison of p.m.r. spectra in deuteriochloroform and in trifluoroacetic acid-*d*, see Table 1) favors **4** as majority species. The calculated bond orders for the 2–3 bond in **4** as compared with **1** increase significantly (from 0.676 to 0.720), with but little change in the bond orders on the periphery of the pyrimidine moiety; for the model comparison of **5** with **1**, the bond orders where proton–proton coupling would be detectable are closely similar for each species.

The changes in coupling constants accompanying protonation are confined to an increase in J_{23} from 2.0 to 3.0 Hz, whereas J_{56} and J_{67} are unaffected; in view of previously demonstrated bond order – coupling constant relationships (15, 16), this pattern is consistent with **4** but not with **5**. The increase in bond order between atoms 2 and 3 may be understood in resonance formalism by considering the contribution of structure **4***a*. Related evidence supporting position 1 as the protonation site is provided by the lanthanide-induced shifts of the protons in **1**, where the pattern of shifts indicates almost exclusive complexation at nitrogen-1 (unpublished work with Mr. Philip Smith).

Accepting that the predominant conjugate acid species of **1** is **4**, we have modelled the expected site of electrophilic substitution in **4** by evaluating the HMO localization energies for substitution at positions 3 and 6, taking cation–cation repulsion into account by a summation procedure (17, 18). 3-Substitution is strongly favored (the localization energies are 2.04 β for 3-substitution and 2.39 β for 6-substitution) and although the cation–cation repulsions favor 6- over 3-substitution the difference in repulsions is only *ca.* 20 kJ M^{-1} and is not sufficient to counterbalance the difference in σ-complex energies. Similarly, the higher-level CNDO/2 calculations of the relative binding energies for 3- and 6-proton exchange intermediates (σ-complexes for proton exchange) involving each of the species **1** and **4**, give energy differences of 107 kJ M^{-1} favoring

TABLE 1. Proton magnetic resonance spectra of pyrazolo[1,5-*a*]pyrimidine and derivatives

Species	Solvent	Chemical shifts for protons[a]					Coupling constants (Hz)			
		2	3	5	6	7	J_{23}	J_{56}	J_{67}	J_{57}
1	$CDCl_3$	8.13	6.72	8.69	6.80	8.47	2.0	5.0	7.0	2.0
	$CDCl_3$:DMSO-d_6 (9:1)	8.11	6.65	8.93	6.86	8.50	2.0	4.8	7.0	2.0
	TFA-*d*	8.75	7.32	9.88	7.72	9.20	3.0	5.0	7.0	2.0
2*a*	DMSO-d_6	9.07	—	9.43	7.50	9.03	—	4.0	7.0	2.0
3*a*	DMSO-d_6	8.60	7.02	10.25	—	9.20	2.0	—	—	1.9
2*b*	$CDCl_3$:DMSO-d_6 (9:1)	8.23	—	8.92	7.08	8.65	—	4.0	7.0	2.0
3*b*	$CDCl_3$:DMSO-d_6 (9:1)	8.10	—	8.97	—	8.53	—	—	—	2.0

[a]In p.p.m. downfield from internal tetramethylsilane.

3-substitution in species **1** and 35 kJ M^{-1} favoring 3-substitution in species **4**. Both theoretical approaches agree in suggesting that 3-substitution will be the normal pattern for electrophilic substitution in pyrazolo[1,5-*a*]-pyrimidine, for reaction through either the conjugate acid **4** or the free base **1**.

This leads to the conclusion that the 6-nitration observed using the nitric acid – acetic anhydride reagent is not a simple displacement of a proton by nitronium ion. Since it is known that this reagent often adds the elements of nitronium acetate to bonds of high order in olefinic and heteroaromatic species (10, 19), we propose that formation of the 6-nitro compound **3***a* results from rapid addition of nitro and acetate moieties to the 6—7 bond of **1** to yield the adduct **6** (reaction through the free base **1** is suggested since this will be present in significant proportions in the reaction medium); **6** is postulated to yield **3***a* by elimination of acetic acid during work-up. The rate of formation of **6** from pyrazolo[1,5-*a*]pyrimidine is postulated to be faster than the encounter rate of nitronium ion with substrate, in order to account for the absence of 3-nitration. Evidence supporting the postulated intermediacy of **6** is cited in the Experimental section.

Proton Magnetic Resonance Spectra

The data assembled in Table 1 for the various pyrazolo[1,5-*a*]pyrimidines reveal that the 3- and 6-protons in **1** have characteristic chemical shifts and interprotonic couplings: species carrying substituents at these positions lack these characteristic signals. The nitro group in **2***a* and **3***a* exerts the expected deshielding influence on vicinal protons (20), whereas bromo substituents (as in **2***b* and **3***b*) have little effect on the shifts of the remaining protons, again in accord with expectation (20).

The sequence of chemical shifts for the protons of pyrazolo[1,5-*a*]pyrimidine in trifluoroacetic acid-*d* follows the order of calculated HMO π-electron densities for the 1-protonated species **4** if the shifts are corrected for ring-current and anisotropy effects (*cf.* 21): the equation linking these quantities is

$$\delta = 15.31 - 6.92q_\pi$$

$$(n = 5, r = 0.968)$$

and the response in p.p.m./electron is in the range typical of aromatic protons (21).

Experimental

Microanalyses were carried out using a Hewlett-Packard Model 185 Analyzer. Melting points were measured on a Kofler Heizbank and are corrected with reference to standard samples. The p.m.r. spectra were recorded with a Varian A-60D spectrometer, equipped with a V-6040 variable temperature controller. Infrared spectra were obtained on a Beckman Acculab 4 spectrometer.

Synthesis of Pyrazolo[1,5-a]pyrimidine, 1

3-Aminopyrazole-4-carboxylic acid (Aldrich Chemical Co.) (5 g) was decarboxylated by heating at *ca.* 170° until evolution of carbon dioxide ceased. The decarboxylation product was dissolved in ethanol (75 ml) and to this solution was added 10 *M* hydrochloric acid (5 ml) and zinc chloride (2.5 g). The mixture was heated to reflux and a solution of 1,1,3,3-tetramethoxypropane (6.6 g) in ethanol (10 ml) was added; heating under reflux was continued for 1 h. The reaction mixture was poured onto ice water (500 g), neutralized with aqueous ammonia, and extracted with chloroform (4 × 100 ml). Removal of the chloroform under reduced pressure, followed by vacuum sublimation at *ca.* 80°, provided pyrazolo[1,5-*a*]pyrimidine **1**, m.p. 105° (4.0 g, 86% based on 3-aminopyrazole-4-carboxylic acid).

Anal. Calcd. for $C_6H_5N_3$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.60; H, 4.25; N, 35.15.

Nitrations

To 3-Nitropyrazolo[1,5-a]pyrimidine, 2a

Pyrazolo[1,5-*a*]pyrimidine (1.19 g, 0.01 mol) was dissolved in concentrated sulfuric acid (*d* 1.84, 10 ml) at 20°, cooled to −5°, and treated at this temperature with a mixture of concentrated sulfuric acid and fuming (90%) nitric acids (1:1 v/v; 4 ml). The reaction mixture was kept at 0° for 15 min and at 5° for 15 min, and poured onto ice. The precipitated light yellow solid was collected by filtration, washed with cold water, and crystallized from water, yielding 623 mg 3-nitropyrazolo[1,5-*a*]-pyrimidine **2***a*, m.p. 259–260°.

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.91; H, 2.45; N, 34.14. Found: C, 43.59; H, 2.36; N, 33.82.

Extraction of the filtrate with chloroform, followed by evaporation of the extract, yielded recovered pyrazolo-[1,5-*a*]pyrimidine (170 mg); the yield of isolated, crystallized product based upon the apparent conversion is 44%. Monitoring of the p.m.r. spectra of model reaction mixtures using deuterated nitrating media indicated no organic species other than the 3-nitro compound **2***a* and unreacted **1**.

To 6-Nitropyrazolo[1,5-a]pyrimidine, 3a

Pyrazolo(1,5-*a*)pyrimidine (510 mg, 0.005 mol) in acetic anhydride (10 ml) was nitrated by dropwise addition of fuming (90%) nitric acid (5 ml) over 1 h at 0–5°. The reaction mixture was poured onto crushed ice and allowed to stand overnight. The precipitate was collected and crystallized from methanol, yielding 6-nitropyrazolo-[1,5-*a*]pyrimidine **3***a*, m.p. 180° (300 mg, 43% of crystallized product).

Anal. Found: C, 43.50; H, 2.71; N, 34.30.

The p.m.r. spectrum of the crude product showed no indication of the presence of the 3-nitro compound **2***a*. Marginally successful efforts were made to demonstrate

the intermediacy of the addition product **6** in yielding **3***a*, as follows: removal of the volatile materials from an aliquot portion of a reaction mixture by low-temperature vacuum distillation left yellow oily material, which was extracted with chloroform-*d* at 5°; the extract was washed repeatedly with ice-cold aqueous sodium hydrogen carbonate, dried overnight over anhydrous magnesium sulfate at 5°, and concentrated at 5° under reduced pressure. The p.m.r. spectrum of the concentrate was recorded using a probe temperature of 0°; it showed signals of similar intensity at δ 7.90 and 7.84, assigned, respectively, to acetate methyl groups in residual acetic acid (or acetic acid from the decomposition of **6**) and to the species **6** (*cf.* the chemical shift of acetate methyl signals in a related adduct isolated in the acetyl nitrate nitration of 4-phenylpyrimidine (10)). The aromatic region showed 17 signals between 400 and 600 Hz from tetramethylsilane, consistent with the presence of **1**, **3***a*, and **6**; resolution was limited by peak half-widths of 2–3 Hz but subtraction of signals assignable by inspection to **1** and **3***a* (compare Table 1) suggested the following chemical shifts for the protons of **6**: δ 8.4 (2-proton), 7.3 (3-proton) 9.5 (5-proton), 8.0 and 8.2 (6- and 7-protons). After standing overnight, the p.m.r. spectrum of this sample indicated the presence of **1**, **3***a*, and acetic acid. A further portion of the chloroform-*d* concentrate was used to obtain a rapid-scan i.r. spectrum. By comparison with spectra of authentic samples of **1** and **3***a*, it was evident that these were major components but carbonyl absorptions were also present at 1750 (s) and 1700 cm^{-1} (vs); the high-frequency peak is in the region expected (*cf.* (10)) for the *C*-acetate group of **6** (the 1700 cm^{-1} absorption is due to the acetic acid).

Brominations

To 3-Bromopyrazolo[1,5-a]pyrimidine, 2b

Pyrazolo[1,5-*a*]pyrimidine (1.19 g, 0.01 mol) was brominated using a stoichiometric amount of bromine in chloroform at room temperature for 1 h. The reaction mixture was washed with aqueous sodium hydrogen carbonate and the chloroform layer was separated and evaporated, leaving crude 3-bromopyrazolo[1,5-*a*]pyrimidine, which was crystallized from water to give pure **2***b*, m.p. 158–159° (1.00 g, 50%).

Anal. Calcd. for $C_6H_4BrN_3$: C, 36.36; H, 2.02; N, 21.21. Found: C, 36.05; H, 2.05; N, 21.40.

To 3,6-Dibromopyrazolo[1,5-a]pyrimidine, 3b

To a stirred solution of pyrazolo[1,5-*a*]pyrimidine (1.19 g, 0.01 mol) in ethanol (25 ml) was added, dropwise, a saturated aqueous solution of bromine (50 ml). During the addition, nitrogen gas was bubbled slowly through the solution. After addition of the bromine reagent was complete (2 h), the reaction mixture was made basic with aqueous sodium hydroxide, and the precipitated solid was collected. The aqueous filtrate was extracted with chloroform (3 × 100 ml), the chloroform extracts were combined, dried (anhydrous sodium carbonate), and evaporated. The residue was added to the precipitated solid, and the entire material was crystallized from ethanol, yielding 3,6-dibromopyrazolo[1,5-*a*]-pyrimidine **3***b*, m.p. 198–200° (1.40 g, 50%).

Anal. Calcd. for $C_6H_3Br_2N_3$: C, 26.02; H, 1.09; N, 15.18. Found: C, 26.00; H, 1.03; N, 15.09.

Molecular Orbital Calculations

The calculations using the simple Hückel method (HMO) were made using a standard program (10, 21) with an IBM 1130 computer. The electronegativity parameters h for various types of nitrogen were: pyrroloid, $h = 1$; pyridinoid, $h = \frac{1}{2}$. Electrostatic corrections to the localization energies were taken into account as follows (18): the interaction energy between the incoming electrophile and the charge-field of the cationic heterocyclic substrate was calculated for slightly polarized models of the substrate (the Coulomb integral of the carbon under attack was increased from α to $\alpha + \frac{1}{2}\beta$). Corrections were evaluated by summation of the terms q_i/r_i for each atom, using the HMO π-electron densities (q_i is the net charge at a particular atom and r_i its distance from the incoming electrophile, which was assumed to be normal to the aromatic ring plane and 0.3 nm directly above the site of attack).

CNDO/2 calculations were made using a version of Quantum Chemistry Program Exchange Program 91 modified for operation on a Hewlett-Packard 3000 Computer. The bond lengths chosen were as follows: for **1** (bond, bond length) 1—2, 0.132 nm; 2—3, 3—9, 4—9, 4—5, 5—6, 6—7, 0.14 nm; 7—8, 8—9, 0.134 nm; 8—1, 0.145 nm; and for the conjugate acid species **4** and **5**, 1—2, 0.130 nm; 8—1, 0.150 nm; all other ring bonds, 0.140 nm. All aromatic C—H bonds are 0.108 nm; the N—H bond, 0.100 nm. All C—H bonds and the N—H bond bisect the bond angles linking the C or N atoms to the ring system. Bond angles were as follows: for **1** (angle defined by constituent atoms, angle) 9—8—1, 105°; 8—1—2, 112°; 1—2—3, 107°; 2—3—9, 109°; 3—9—8, 109°; 8—4—9, 115°; 9—4—5, 4—5—6, 5—6—7, 6—7—8, 120°; 7—8—9, 125°; and for the conjugate acid species, 9—8—1, 108°, 8—1—2, 106°, 1—2—3, 110°; 2—3—9, 3—9—8, 108°; all other ring angles, 120°.

The σ-complexes from attachment of protons to the 3 or 6 positions of **1** and the conjugate acid **4** were modelled by changing the bond lengths linking the site of proton attachment to the other ring atoms to 0.150 nm, assuming equivalent C—H bonds of length 0.109 nm, and a tetrahedral H—C—H angle; the other angles in the affected ring were adjusted to reform the ring, without variation of bond lengths.

The molecular geometries chosen are based upon those used for a previous study (2) of a closely related condensed pyrazole species, where the choice gave good correspondence with observed dipole moments. Variations for conjugate acid species and for σ-complex models used the standard set of bond lengths and bond angles recommended for the CNDO/2 program.

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