New Heterocyclic Bridgehead Nitrogen Compounds
Synthesis of 1-(p-Tosyl)pyrazolo[1,5-a]pyrimidines and Pyrazolo[5,1-c]-[1,2,4]-triazine Derivatives

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Received 26 March 1992

Interaction of 3-amino-1,5-dihydro-1-(p-tosyl)pyrazole with ethyl acetoacetate, acrylonitrile and acetyl acetone afforded the corresponding 1-(p-tosyl)pyrazolo[1,5-a]pyrimidine derivatives. Diazotization of the starting compound and subsequent coupling with bifunctionally active nitriles yielded the corresponding pyrazolo[5,1-c]-[1,2,4]-triazine derivatives. IR and 1H NMR spectra for all of the hitherto prepared compounds are in good agreement with the proposed structures.

Schistosomiasis is considered to be one of the most difficult diseases to treat [1] and is a national problem in Egypt. Accordingly considerable attention has been directed toward the development of useful chemotherapeutic agents. Perusal of literature reveals the importance of pyrazolo[1,5-a]pyrimidine derivatives, especially those substituted with mercapto group [4, 5], as antischistosomal agents. Thus in continuation of our interest in synthesis of fused and/or isolated pyrimidine derivatives as potential chemotherapeutic agents [6—8], we report herein on the synthesis of new series of substituted pyrazolo-[1,5-a]pyrimidine derivatives and their aza analogues, namely, pyrazolo[5,1-c]-[1,2,4]-triazines that accommodate the pharmacologically active tosyl moiety aiming to synthesize novel products of extended and/or improved antischistosomiasis activity.

The synthesized compounds possess latent functional substituents and appear promising for utility in further chemical transformations and biological studies.

The general synthetic sequence followed for the preparation of these compounds is outlined in Scheme 1.

**EXPERIMENTAL**

Melting points are not corrected. The IR spectra (KBr) were measured on spectrophotometer SP 2000 (Pye—Unicam). The 1H NMR spectra (CDCl3) were recorded on spectrometer EM 360 (Varian; 60 MHz) with TMS as an internal standard.

7-Methyl-1,2,4,5-tetrahydro-1-(p-tosyl)pyrazolo-[1,5-a]pyrimidin-5-one ([II])

A mixture of 3-amino-1,5-dihydro-1-(p-tosyl)-pyrazole ([II]) (0.01 mol) and ethyl acetoacetate (0.01 mol) was heated for 10 h at 160 °C. The reaction mixture was cooled, triturated with ethanol and the resulting solid product was crystallized from DMF—ethanol mixture to give [II] as yellow crystals in 63 % yield, m.p. = 210 °C. For C14H15N3O3S: calcd: 55.1 % C, 5.0 % H; found: 54.7 % C, 4.9 % H. IR spectrum, ν/cm−1: 3300 ν(NH), 1680 ν(amidic CO), 1640 ν(C=C), 1350 ν(SO2), 1150 ν(SO3). 1H NMR spectrum, δ (CDCl3): 1.9 and 2.3 (s, s, 6H, 2 × CH3), 2.56 (d, 2H, CH2), 5.40 (t, 1H, CH), 5.75 (s, 1H, C-6—H), 6.5—7.4 (m, 4H, H arom), 9.1 (br s, 1H, NH).

1,2-Dihydro-5,7-dimethyl-1-(p-tosyl)pyrazolo-[1,5-a]pyrimidine ([IV])

Compound [II] (0.01 mol) was condensed with acetyl-acetone (0.01 mol) utilizing the same experimental procedure as described above. The resulting product was crystallized from dioxane as yellow crystals in 63 % yield, m.p. = 198 °C. For C15H17N3O2S: calcd: 59.4 % C, 5.7 % H; found: 58.9 % C, 5.6 % H. IR spectrum, ν/cm−1: 1640 and 1620 ν(C=N and C=C), 1310 ν(SO2), 1155 ν(SO3). 1H NMR spectrum, δ (CDCl3): 1.95 (s, 6H, 2 × CH3 of pyrimidine moiety), 2.3 (s, 3H, tosyl—CH3), 2.6 (d, 2H, CH2), 5.45 (t, 1H, CH), 5.75 (s, 1H, C-6—H), 6.5—7.4 (m, 4H, H arom).

3-Bromo-1,2-dihydro-5,7-dimethyl-1-(p-tosyl)pyrazolo-[1,5-a]pyrimidine ([V])

To a suspension of [IV] (0.01 mol) in carbon tetrachloride (50 cm3) N-bromosuccinimide (0.013 mol) was added. The reaction mixture was heated at 60 °C and kept at this temperature for 15 min. Trituration with petroleum ether afforded the required product.
product as yellow crystals in 77% yield, m.p. = 178 °C. For C_{15}H_{16}BrN_{3}O_{2}S, w_{i}(calc.): 47.1% C, 4.2% H; w_{i}(found): 46.9% C, 3.8% H. \(^1\)H NMR spectrum, δ: 1.95 (s, 6H, 2 × CH₃ of pyrimidine moiety), 2.3 (s, 3H, tosyl—CH₃), 2.65 (s, 2H, CH₂), 5.7 (s, 1H, C-6—H), 6.4—7.4 (m, 4H, H_{arom}).

1,2-Dihydro-5,7-dimethyl-3-isothiocyanato-1-(p-tosyl)pyrazolo[1,5-a]pyrimidine (VI)

A solution of V (0.01 mol) in ethanol (50 cm³) was treated with potassium thiocyanate (0.01 mol) dissolved in water (5 cm³). The reaction mixture was
RESULTS AND DISCUSSION

Fusion of equimolar quantities of the ρ-tosyl aminopyrazole derivative (I) and ethyl acetoacetate at 160 °C yielded only one isolable product that was analyzed correctly for a molecular formula of C18H13N3O5S. The structure of this product may be formulated as II or its isomeric structure III (Scheme 1). Although structure III seemed convincing, depending on similarity to the well established behaviour of 5-aminopyrazoles towards β-keto esters [9], structure II was considered most likely based on spectral evidences, besides the characteristic absorption band at $\tilde{\nu} = 3300 \text{ cm}^{-1}$ for NH group, IR spectrum for this product revealed another strong absorption at $\tilde{\nu} = 1680 \text{ cm}^{-1}$ that might be ascribed to the ring carbonyl (amidic CO). For structure III, the band corresponding to the ring-carbonyl group should be obtained at higher wavenumber (e.g. 1700 cm$^{-1}$) [10].

Moreover, $^1$H NMR spectrum of this pyrazolo-[1,5-a]pyrimidine derivative revealed two one-proton singlets at $\delta = 5.75$ and 9.10 that might be attributed to pyrimidine ring CH and NH protons, respectively. For structure III, a group signal at about $\delta = 4.00$ (two methylene group protons), similar to that previously reported, would have been expected [11, 12].

Chemical evidences that support structure II were drawn from the fact that the obtained product failed completely to undergo condensation reactions with aromatic aldehydes or to couple with benzene—diazonium salt solutions, reactions which proceed readily with activated methylene and methine functions, respectively, as in case of the pyrazolo-pyrimidine derivative IIIa and/or its tautomeric structure IIIb which accomodate the activating cyclic tertiary amidic linkage.

Similar to the well known behaviour of 3- or 5-aminopyrazoles, compound I condensed with acetylacetone to yield the corresponding pyrazolo-[1,5-a]pyrimidine derivatives IV. The structure of this product was inferred from analytical and spectral data (cf. Experimental).

Compound IV could be converted into V through treatment with N-bromosuccinimide (NBS). The latter derivative reacted readily with potassium thio-cyanate to yield the corresponding isothiocyanate derivative VI. The presence of isothiocyanate function was inferred from IR spectral data which revealed the presence of an intense and broad absorption band at $\tilde{\nu} = 2130 \text{ cm}^{-1}$ corresponding to stretching vibration of this moiety.

Compound I reacted also readily with acrylonitrile to yield a 1:1 adduct. However, in contrast to the expected cyanoethylation product, the IR spectrum of the obtained compound revealed the absence of absorption bands that might be ascribed to the cyano

5-Amino-1,2,6,7-tetrahydro-1-(ρ-tosyl)pyrazolo-[1,5-a]pyrimidine (VIII)

To a solution of acrylonitrile (0.01 mol) in pyridine (15 cm$^3$), compound I (0.01 mol) was added and the reaction mixture was boiled under reflux for 6 h and concentrated under reduced pressure. Trituration with ethanol followed by allowing the mixture to stand at ambient temperature for 24 h afforded the product which was filtered and recrystallized from ethanol (yellow crystals) in 74 % yield, m.p. = 184 °C. For C13H16N2O2S $w_1$(calc.): 53.4 % C, 5.5 % H; $w_1$(found): 53.4 % C, 5.3 % H. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 3100—3500 $\nu$(NH and NH), 1310 $\nu$(C—S), 1160 $\nu_s$(SO2), 1155 $\nu_s$(SO2).

7-Substituted 6-Cyano-1,2-dihydro-1-(ρ-tosyl)pyrazolo[5,1-c]-[1,2,4]triazines Xa—Xc

A cold diazonium salt solution, prepared from I (0.01 mol), was poured gradually with continuous stirring into a cold mixture of the appropriate active hydrogen reagent (0.01 mol) in ethanol (20 cm$^3$) in the presence of sodium acetate solution (1 g dissolved in 5 cm$^3$ of water). The reaction mixture was stirred at room temperature for 2 h and the solid product so formed was crystallized from ethanol as yellow to orange crystals in an average good yield (69—76 %).

Xa: M.p. = 230 °C. For C19H18N2O2S $w_1$(calc.): 60.5 % C, 4.0 % H; $w_1$(found): 60.2 % C, 3.9 % H. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 2220 $\nu$(CN), 1640 and 1633 $\nu$(C=C and N=N), 1320 $\nu_{as}$(SO2), 1160 $\nu_s$(SO2).

Xb: M.p. = 195 °C. For C19H18N2O2S $w_1$(calc.): 53.3 % C, 4.2 % H; $w_1$(found): 53.3 % C, 4.0 % H. $^1$H NMR spectrum, $\delta$: 1.9 (s, 3H, CH$_3$), 2.3 (s, 3H, tosyl—CH$_3$), 2.6 (d, 2H, CH$_2$), 5.6 (t, 1H, C-3—H), 6.4—7.3 (m, 4H, H$_{arom}$).

Xc: M.p. = 265 °C. For C19H18N2O2S $w_1$(calc.): 49.4 % C, 3.8 % H; $w_1$(found): 49.6 % C, 3.65 % H. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 3380—3450 $\nu$(NH$_2$), 2225 $\nu$(CN), 1640 $\nu$(C=C), 1633 $\nu$(N=N), 1320 $\nu_{as}$(SO2), 1155 $\nu_s$(SO2).
group. Two isomeric structures seemed possible for the produced adduct (cf. structures VII and VIII). Although it is quite difficult to exclude structure VII completely for this product, structure VIII seemed to be more likely, not only on the basis of analogy to the reported behaviour of aminopyrazoles toward activated double bond systems [13—15] where cyanoethylation for such compounds involves the ring atom N-1 and not the amino group [9], but also according to $^1$H NMR spectra which displayed a pattern (cf. Experimental) that could be intelligibly interpreted in terms of the proposed tautomeric structure VIIlb.

Diazotized compound I coupled with benzoylacetonitrile, 3-aminobutyronitrile or malononitrile to yield directly the corresponding pyrazolo[5,1-c]-[1,2,4]-triazine derivatives Xa—Xc. The formation of these fused-ring systems and not the acyclic hydrazones finds support from the previously reported work [5], where the reaction with these reagents was assumed to proceed, most likely, via a (4 + 2) dipolar cycloaddition sequence. The different possible mechanisms for the reaction of diazotized cyclic amidines with active hydrogen reagents have been critically discussed and reviewed [16].

The hitherto prepared products were characterized by elemental analysis and spectral measurements. The possibility of using these compounds as possible chemotherapeutic agents is for the time being under investigation. The results of this study together with toxicity of the prepared compounds will be published elsewhere.

REFERENCES