SYNTHESIS OF 2-AMINO-4,5,7-TRIARYLIMIDAZO[1,5-b]PYRIDAZINES

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The reaction of 4-aryl-1,2-diaminoimidazoles with 1-aryl-2,3-dibromo-3-(4-nitrophenyl)propanones, 2-bromo-1-phenyl-3-(4-chlorophenyl)propenone, and 1,3-diarylpopyrones yields 2-amino-4,5,7-triarylimidazo[1,5-b]-pyridazines. The structure of one of these products was determined by x-ray diffraction analysis.

Diaminoimidazoles hold interest in light of their dual reactivity. Both imidazotriazepins [1, 2] and imidazopyrimidines [3] are formed in their reactions with carbonyl compounds. In the present work, we studied the cyclocondensation of 4-aryl-1,2-diaminoimidazoles (I and II) with chalcone dibromides (IVa-IVh). This reaction was carried out upon heating diamines I and II with ketones IVa-IVh in methanol at reflux for 6-8 h using N-methylmorpholine as the catalyst.

The reaction of aromatic o-diamines with α,β-dibromochalcones proceeds through a series of steps involving formation of an α-bromochalcone as the result of the elimination of HBr, addition of the diamine at the C=C bond to give a β-adduct, and separation of a β-enaminochalcone or the product of its cyclization, namely, 1,5-diazepin, from the reaction mixture [4, 5].

Products Va-Vh and chalcones VIa-Vlh were isolated from the reaction mixture under the conditions described, indicating participation of tertiary amines in the reduction of the resultant α-bromochalcones [6]. This behavior may account for the low yields of Va-Vh. Indirect evidence for initial dehydrobromination of ketones IVa-IVh is found in the formation of Vk in the reaction of diamine III with α-bromochalcone VII. Products Vi and Vj were isolated in satisfactory yield in the reaction of diamines I and II with acetylenic ketones VIII and IX. The IR spectra of these products show bands at 3280 and 3452 cm⁻¹ assigned to primary amino group stretching vibrations and bands at 1637-1652 cm⁻¹ (superposition of stretching bands νCN and νCC). The electronic absorption spectra of imidazopyridazines Va-Vk show a strong band in the vicinity of 290 nm and long-wavelength band at 490-500 nm.

The PMR spectra of Va, Ve, and Vi (see Experimental section) show aromatic proton signals at 6.9-8.2 ppm and a broad singlet at 6.5 ppm assigned to NH₂ group protons, which disappears upon the addition of methanol. The signal for the pyridazine ring proton is sometimes overlapped by the aromatic proton multiplet but is readily determined by analyzing the integral signals.

The mass spectrum of Ve shows quasimolecular ions [M + H]⁺ with m/z 518.9, 520.9, and 522.9, which corresponds to the isotopic composition of the molecule assuming the presence of one bromine atom and one chlorine atom. The mass spectrum also shows fragmentation ions with m/z 504 [M-O]⁺ and m/z 474 [M-NO]⁺.

The stoichiometry of this reaction indicates the loss of two molecules of HBr and one molecule of water in the synthesis of Va-Vk.
Thus, these results indicate cyclocondensation involving only one amino group.

The structures of Va-Vk were determined by x-ray diffraction analysis for the case of Vk, which, according to the data obtained, is 2-amino-7-(p-bromophenyl)-4-(p-methylphenyl)-5-phenylimidazo[1,5-b]pyridazine. The bicyclic imidazopyridazine system in Vk is planar. The amino group nitrogen atom has planar trigonal configuration. The phenyl substituent at C(2) (Fig. 1) is somewhat twisted relative to the plane of the bicyclic system (the N(2)--C(2)--C(19)--C(20) torsion angle is 16.9°), which is likely a consequence of the short intramolecular contacts H(20)...N(2) 2.48 Å (the sum of the van der Waals radii is 2.66 Å [7]) and H(24)...H(3) 2.18 Å (2.32 Å). The conjugation between the π-electron systems of the arene substituents and imidazopyridazine fragment is significantly violated due to twisting of the aromatic rings about C--C bonds (torsion angles C(3)--C(4)--C(13)--C(18) 59.0° and C(5)--C(6)--C(7)--C(12) 46.9°). This twisting is probably a result of the repulsion between these substituents (short intramolecular contacts C(7)...C(14) 3.30 Å (3.42 Å) and C(13)...C(12) 3.28 Å).

The molecules of Vk in the crystal form centrosymmetric dimers due to intermolecular hydrogen bonds H(4a)...N(y) (1 - x, -y, 1 - z) (H--N 2.20 Å, N--H--N 156°). Since the features of Vk are in accord with the data obtained for the other compounds of this series, Va-Vi are also substituted imidazo[1,5-b]pyridazines.

Products V could not be obtained in the reactions of diamines I-III with chalcone dibromides lacking a nitro group in the benzylidene fragment. This failure may be attributed both to the higher rate of HBr elimination in dibromides IVa-IVh and the greater electrophilicity of the β-position of the α-bromo-β-nitrophenylchalcone intermediates.

Thus, diamines I-III in their reactions with ketones IVa-IVh and VII-IX behave as typical 1,3-dinucleophiles. C(5) in the imidazole ring proves most susceptible to electrophilic attack in I-III. Alkylation by the unsaturated ketones occurs specifically at this atom followed by heterocyclization.

This sequence of steps is in good accord with the formation of imidazopyridazine Va in the reactions of hydrazones X-XII with chalcone dibromide IVa in the presence of N-methylmorpholine. The tendency of hydrazones to undergo hydrolysis decreases with increasing electron-withdrawing properties of the aromatic ring in the carbonyl component. Thus, the total rate of the cyclocondensation involving hydrazones X-XII is expected to drop in the series: XI (R' = NMe2) > X (R' = H) > XII (R' = NO2). For example, trace amounts of product Va are detected chromatographically in the case of hydrazone XII only after 14 h heating at reflux in 1:1 DMF-MeOH.