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Unexpected transamination between 2-aminoazoles and *N*-iodoacetyl azoles

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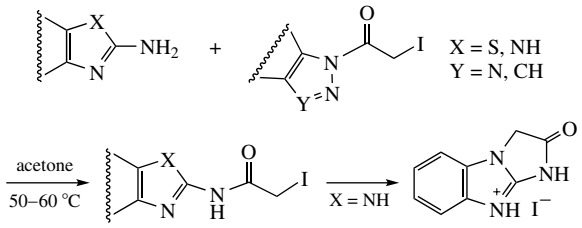
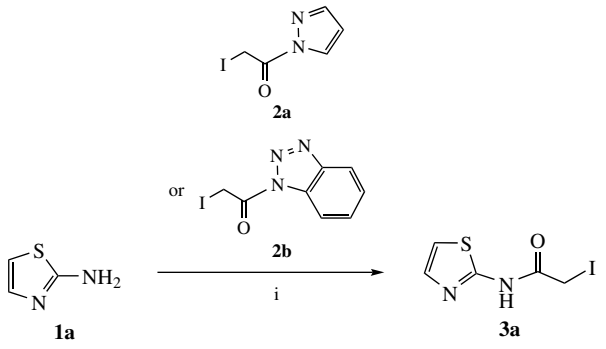
***N*-Iodoacetyl-substituted azoles undergo transfer of iodoacetyl group from heterocyclic N atom toward the amino group of amino azoles, unlike the earlier investigated iodomethyl ketones. The proposed mechanism explaining the observed difference in such transamination is confirmed by calculations. The product derived from 2-aminobenzimidazole is cyclized into fused imidazo[1,2-*a*]benzimidazol-9-ium salt.**



Keywords: aminoazoles, iodoacetyl azoles, transamination, cyclization, imidazo[1,2-*a*]benzimidazol-9-ium salts, quantum chemical calculations.

α-Haloalkyl ketones are the known synthons for the design of various heterocyclic compounds, including fused heterocycles, possessing a wide spectrum of biological properties. Thus, heteroaromatic systems containing thiazole, benzothiazole, and benzimidazole backbones, are recognized as privileged pharmacophores for the design of pharmaceutical drugs.[1–9] Recently,[10] we have synthesized heterocyclic molecular hybrids and obtained linear and cyclic salts based on the 2-aminobenzothiazolium cations, which can be recommended for the design of low-toxic drugs possessing anti-ischemic activity and regulating the action of glycosylphosphatidylinositol phospholipase D enzyme (GPI).

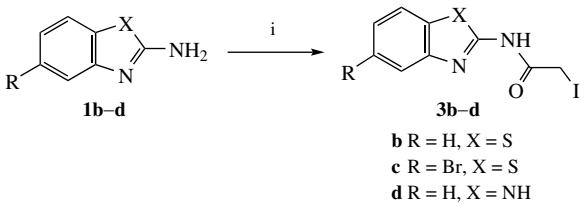
The goal of the present work was to expand this approach to other substrates. The choice of the substrates was based on their suitability for the synthesis of practically important compounds. For this purpose, reactions of 2-aminothiazole **1a** and its benzo-fused analogues **1b–d** with 1-(1*H*-1,2,3-benzotriazol-1-yl)-2-iodoethan-1-one **2a** or 1-(1*H*-pyrazol-1-yl)-2-iodoethan-1-one **2b** were investigated (Schemes 1 and 2). Earlier, we have successfully used compound **2a** in the synthesis of the azole derivatives with five-membered N-heterocyclic ring.[11] The reaction of 2-aminothiazole **1a** with compound **2a** was carried out in acetone on heating (see Scheme 1).†



Scheme 1 *Reagents and conditions*: i, acetone, 50 °C, 5 h.

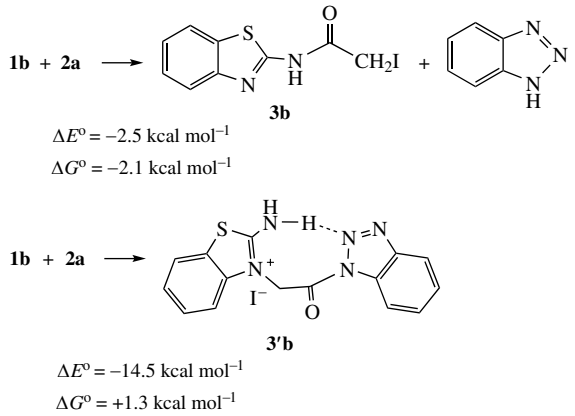
Surprisingly, instead of the expected products of N-alkylation of the imine nitrogen in **1a** as was in the case of iodomethyl ketones,[10] 2-iodo-*N*-(1,3-thiazol-2-yl)acetamide **3a** with the amide fragment was obtained. Pure product **3a** was precipitated after the completion of the reaction; the yield was 76% and no additional purification was needed. {^{1}H–^{13}C} HSQC NMR spectra of compound **3a** did not contain cross-peaks between protons at 4.5–6.0 ppm and the methylene carbon atom at 50–60 ppm typical for the *N*-ketoalkylated product; instead, the signals for the CH_2I group at 3.91 (^{1}H) and –1.18 ppm (^{13}C) were present. A similar exchange reaction occurs with compound **2b** giving the same product **3a** in 54% yield (see Scheme 1). High nucleofugality of benzotriazole group at the carbonyl carbon is well known,[12–14] which is employed in the synthesis of various products containing peptide bonds, including heterocyclic compounds.

The generality of such a transamination reaction with iodoacetyl azoles was exemplified on the reactions of **2a** with 2-aminobenzothiazoles **1b**,**c** and 2-aminobenzimidazole **1d**,



Scheme 2 *Reagents and conditions*: i, **2a** or **2b**, acetone, 50–60 °C, 5–7 h.

† *General procedure for the synthesis of compounds* **3a–d**. A mixture of 2-aminothiazole **1a** (100 mg, 1 mmol) [or 2-aminobenzothiazole **1b** (150 mg), 2-amino-5-bromobenzothiazole **1c** (230 mg), 2-aminobenzimidazole **1d** (130 mg)] and an equimolar amount of 1-iodoacetyl-substituted azole **2a** (290 mg) [or **2b** (240 mg)] in dry acetone (2 ml) was stirred at 50–60 °C for 5–7 h. The precipitated products **3a–d** were collected, washed with acetone (2 × 5 ml) and diethyl ether (2 × 5 ml) and dried under vacuum.

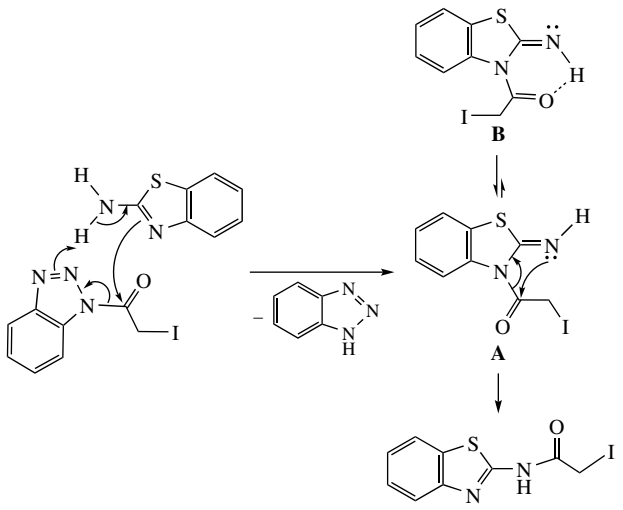


Scheme 3

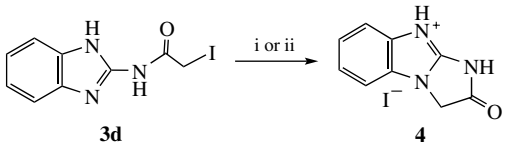
which afforded *N*-(iodoacetyl)amino derivatives **3b**–**d** in 74, 72, and 75% yields, respectively (see Scheme 2). In case of **2b** as the reagent, the yields of products **3b**–**d** were somewhat lower, namely, 50, 48.5 and 52%, respectively. Compound **3d** was reported in a recent paper[8] but not characterized sufficiently. Also, the ^{13}C NMR signal for the methylene carbon in compound **3d** was incorrectly reported to be at 29.04 ppm,[8] whereas our value of 0.34 ppm seems more proper. As for analogue **2a**, its CH_2I carbon resonates upfield at –5.06 ppm while the simulated value is –3.68 ppm.

To get a deeper insight into the origin of the striking difference between the above reactions (Schemes 1 and 2) and the earlier studied reactions with iodoacetone or its analogues with the C–C(O) bond, and having no N–C(O) bond, we have calculated the energies ΔE^o and Gibbs free energies ΔG^o for two alternative reactions leading to the products of transamination (**3b**) and alkylation (**3′b**), as depicted in Scheme 3. The calculations were performed at the B3LYP/DGDZVP level with geometry optimization without any restrictions.[15] Both reactions are exothermic, but while transamination is also exergonic, *N*-alkylation is endergonic and thus prohibited in full agreement with the experiment. The difference between ΔE^o and ΔG^o for *N*-alkylation is due to the entropy loss for the formation of **3′b**.

A tentative mechanism for the formation of *N*-iodoacetyl amides **3** with elimination of the heterocycle molecule is depicted in Scheme 4 on the example of benzotriazole. Initially, the acyl group is transferred to the substrate by the nucleophilic attack of more basic iminium nitrogen ($q_{=N}$ –0.260, q_{NH_2} 0.042) on the carbonyl group. In intermediate **A** the basicity of the



Scheme 4



Scheme 5 *Reagents and conditions*: i, MeOH, 40 °C; ii, DMSO, room temperature.

exocyclic nitrogen (q_N –0.529, q_{NH} –0.198) becomes higher or close to that of the amide nitrogen (q_N –0.241) allowing the transfer of the iodoacetyl residue and formation of the final product. Remarkably, conformation **A** (the global minimum on the potential energy surface), favorable in the orientation of the iminium lone pair for such a transfer, is 4.60 kcal mol^{-1} more stable than conformation **B** (local minimum), in spite of the intramolecular hydrogen bond in the latter, which indirectly confirms the proposed mechanism.

Chloromethyl derivatives of amides containing heterocyclic fragments are actively used in the synthesis of biologically active compounds and pharmaceutical substances.[16–19] The main method for their synthesis is the acylation of amino derivatives of heterocyclic compounds with chloroacetyl chloride.[8,20] Here, we have shown the possibility of the synthesis of iodomethylated amides of 2-aminothiazoles and 2-aminobenzimidazoles by transamination.

The increased interest in the salts of heterocyclic compounds due to their use in different fields of science and technology,[21–23] prompted us to synthesize the fused salt, 2-oxo-2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazol-9-ium iodide **4**. In fact, compound **3d** when slightly heated in methanol for 3 h or stored in DMSO at room temperature for 7 h in the absence of bases or catalysts, undergoes cyclization to salt **4** (Scheme 5). The PASS program (Prediction of Activity Spectra for Substances) indicates a high probability for compound **4** to inhibit the processes of peroxide oxidation of membrane lipids, and to be an antagonist of nicotinic α2β2-receptors (*Pa* = 0.814 and 0.833).[24]

To summarize, a new reaction of transamination of aminoazoles with *N*-iodoacetyl-substituted azoles affords heterocyclic compounds containing the *N*-(iodoacetyl)amino group. Such products can be involved in the side-chain modification reactions, as demonstrated on the example of the synthesis of fused 2-oxo-2,3-dihydro-1*H*-imidazo[1,2-*a*]-benzimidazol-9-ium salt in the absence of bases or catalysts. The results of our ongoing studies will be published elsewhere.

This work was performed using analytical equipment of the Baikal Center for Collective Use of the Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data (synthetic details, spectral characteristics of the products, NMR and mass spectra) associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.039.

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