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New, simple and efficient method for the synthesis of imidazo-azines by flash vacuum thermolysis of *tert*-butylimines of pyrimidine-2-, pyrazine-2-, quinoline-2-, quinoxaline-2- and isoquinoline-1-carbaldehydes

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ABSTRACT

Flash vacuum thermolysis reactions of *N*-(*tert*-butyl)-*N*-(pyrimidin-2-ylmethylidene)amine (**1**), *N*-(*tert*-butyl)-*N*-(pyrazin-2-ylmethylidene)amine (**2**), *N*-(*tert*-butyl)-*N*-(quinolin-2-ylmethylidene)amine (**3**), *N*-(*tert*-butyl)-*N*-(quinoxalin-2-ylmethylene)amine (**4**) and *N*-(*tert*-butyl)-*N*-(isoquinolin-2-ylmethylidene)amine (**5**) have been investigated. The formation of 3-methyl-imidazo[1,5-*a*]pyrimidine(**6**), 3-methyl-imidazo[1,5-*a*]pyrazine (**7**), 1-methyl-imidazo[1,5-*a*]quinoline (**8**), 3-methyl-imidazo[1,5-*a*] quinoxaline (**9**) and 3-methyl-imidazo[5,1-*a*]isoquinoline (**10**) as reaction products was observed. Excellent yields of imidazoazines from monocyclic imines **1** and **2** were found, whereas from bicyclic imines **3–5** slightly lower yields (50–75%) of the major products and formation of byproducts such as quinolone and isoquinoline were observed. These cyclizations were found to occur fully regioselectively onto the nitrogen atom of the adjacent ring. UV-photoelectron spectroscopy combined with FVT and quantum chemical calculations were applied for direct monitoring and characterization of the thermolysis products. The proposed mechanism of these reactions are substantiated by DFT calculations.

1. Introduction

Heteroaromatic *N*-fused bicyclic systems containing the imidazo[1,5-*a*]azine motif (Fig. 1) have many applications in materials chemistry [1,2] and as potent pharmacophores [3–7].

For example, the imidazo[1,5-*a*]pyridine skeleton has potential applications in organic light-emitting diodes (OLEDs) and organic thin layer field-effect transistors (FETs) [8–14]. This aza-heteroaromatic system embedded in biologically active molecules also plays an important role as cardiotonic agents [15], aromatase inhibitors in estrogen-dependent diseases [16], thromboxane A2synthetase inhibitors [17] and angio-tensin II receptor antagonist [18]. Imidazopyridinyl-1,3,4-oxadiazole conjugates are apoptosis inducers and topoisomerase IIα inhibitors [19].

Imidazopyrazine is an important pharmacophore [20–27] prevalent in a number of biologically active molecules. For example, imidazo[1,2-*a*]pyrazine is used as a potent inhibitor of the gastric acid pump [20], kinase aurora inhibitors [21], phosphodiesterase inhibitors [22] and can be used in the treatment of schizophrenia [23]. Imidazo[1,5-*a*]pyrazines are orally efficacious inhibitors of mTORC1 and mTORC2 [24]. They are used as corticotropin releasing hormone receptor ligands [25] and as an agent for the treatment of acute ischaemic stroke [26]. Morever, 1,3-disubstituted imidazo[1,5-*a*]pyrazine may be applied as inhibitors of insulin-like growth-factor IGF-IR [27].

Imidazo[1,5-*a*]pyrimidines exhibit biological activities such as treatment and prevention of diseases mediated by GABA receptors

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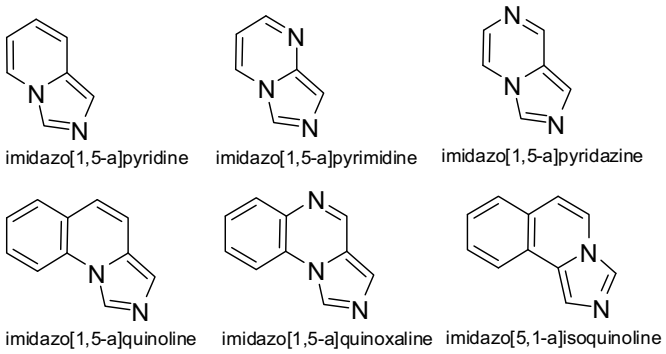
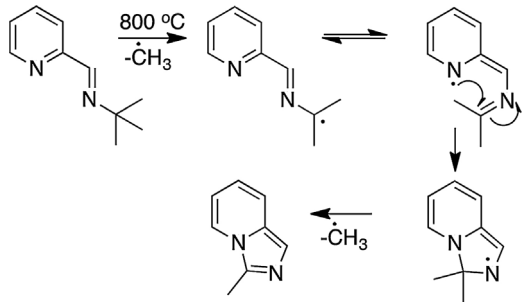


Fig. 1. Imidazo[1(5),5(1)-*a*]azines.



Scheme 1. The mechanism of formation of 3-methylimidazo[1,5-*a*]pyridine.

α-1 and α-2 subunits [28] and metabotropic glutamate receptor antagonist [29]. Several imidazo[1,5-*a*]pyrimidine derivatives demonstrated potent RORc inverse agonist activity in biochemical and cellular assays [30].

The benzologue of imidazo[1,5-*a*]pyridine, i.e. imidazo[1,5-*a*]quinoline, is a significant moiety of NK1 receptors ligands [31], whereas imidazo[1,5-*a*]quinoxaline is the skeleton for inhibitors targeting phosphodiesterase 10A [32,33]. Moreover, imidazo[1,5-*a*]quinoxalines are effective as irreversible BTK inhibitors for the treatment of rheumatoid arthritis [34]. A series of imidazo[1,5-*a*] quinoline derivatives was designed and synthesized for use as central benzodiazepine receptors (CBR) ligands [35].

Despite the importance in the aforementioned subjects, a limited number of synthetic routes are available for these compounds [13,36–42]. Recently, we demonstrated [43–45] a new cyclization of conjugated *tert*-butylimines under flash vacuum thermolysis (FVT) conditions. Thus, thermolysis of *N*-(*tert*-butyl)-*N*-(pyridyn-2-ylmethylidene)amine at 800 °C and 10^{-4} hPa affords 3-methylimidazo[1,5-*a*]pyridine in 80% yield (Scheme 1). The reaction was proposed to proceed by initial elimination of a methyl radical from the *tert*-butyl group, which has a calculated activation barrier of about 70 kcal/mol. This would yield a resonance-stabilized azaallyl radical (Scheme 1). Thanks to the presence of the pyridine-nitrogen atom, a facile ring closure to a cyclic aminyl intermediate can occur. The entire process requires sequential elimination of two methyl radicals.

This mechanism was supported by the calculated energy profile [44]. Other potential reaction paths have been and will continue to be investigated computationally. The alternate, initial elimination of two methyl groups to form an imino(methyl)carbene was found to have a forbiddingly high calculated activation energy (119 kcal/mol). It should be stressed that the reaction (Scheme 1) is fully regioselective, i.e. only cyclization onto the ring nitrogen atom adjacent to the imine moiety takes place. In contrast, in the absence of the α–nitrogen atom, the 3- and 4-pyridine-*tert*-butylimines react differently with more complicated mechanisms [45].

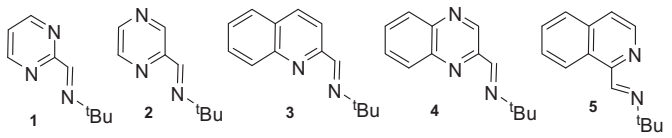


Fig. 2. New *tert*-butylimines.

The foregoing results inspired us to investigate the FVT of *tert*-butylimine derivatives of pyrimidine, pyrazine, quinoline, isoquinoline and quinoxaline (Fig. 2).

The preparative FVT studies were enhanced with UV-photoelectron spectroscopy (UV-PES) combined with online FVT for characterization of the thermolysis product. DFT [ΔSCF+TDDFT (CAM-B3LYP)] calculations of ionization energies using the 6–311G(d,p) basis set were carried out on the optimized geometries of each compound for the reliable assignment of PE bands. DFT calculations of the proposed reaction mechanisms were also performed at the CAM-B3LYP/6-311G(d,p) level.

2. Experimental

2.1. General

All reagents were purchased from commercial suppliers and used without further purification. The ^{1}H- and ^{13}C NMR spectra were recorded with Bruker Avance III apparatus at 600/150 (^{1}H/^{13}C) MHz with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Chemical shifts are reported in ppm, and coupling constants *J* are estimated by first order analysis and given in Hz. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet. Melting points were measured in open capillaries with a MeltTemp apparatus and are uncorrected. IR spectra were recorded for KBr pellets with a Thermo-Nicolet Nexus FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded by the Central Analysis Laboratory of the Polish Academy of Science (Łódź) with a FinniganMAT 95 double focusing spectrometer. Accurate mass measurements were performed by peak matching by using perfluorokerosene as an internal standard. Gravitational column chromatography was performed with Merck silica gel 60 (70–230 mesh). Preparative TLC was performed with plates coated with Merck silica gel 60 (PF_{254}) and a suitable developing solvent system.

2.2. Starting materials

tert-Butyl(quinolin-2-ylmethylene)amine (**3**) was prepared according to the literature protocol [46].

2.3. Synthesis of imines ***1***, ***2***, ***4***, and ***5***

General procedure [47]. The relevant aldehyde (0.025 mol) was dissolved in an excess of *tert*-butylamine (0.193 mol, 14.05 g, 21 ml). Molecular sieves (2–3 g, 4 Å) were added, and the mixtures was stirred at room temperature overnight. Then the mixture was filtered, the molecular sieves were washed with chloroform, and the filtrate was concentrated. The residue was vigorously stirred with hexane (10 ml) and active carbon. The mixture was filtered with celite and washed with hexane. The solution was evaporated under pressure to give the corresponding imine.

2.3.1. N-(tert-*Butyl*)-N-*(pyrimidin-2-ylmethylidene)amine (**1**)*

Yield: 1.29 g (32%), yellow oil, which crystallizes in the fridge. FT-IR (film): $\nu_{C=N}$ 1651 cm^{-1}.^{1}H NMR: δ = 1.37 (s, 9H), 7.28 (t, 1H, *J* = 4.85 Hz), 8.41 (s, 1H), 8.85 (d, 2H, *J* = 4.85 Hz) ppm. ^{13}C NMR: