

Full Paper

Reaction of Nitrilimines with 2-Substituted Aza-heterocycles. Synthesis of Pyrrolo[1,2-*a*]pyridine and Pyrimido[2,1-*d*]1,2,3,5-tetrazine

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Abstract: The reaction of nitrilimine **6a** with ethyl pyridine-2-acetate (**7**) gave the corresponding pyrrolo[1,2-*a*]pyridine **8**, while the reaction of **6b** containing an ester moiety afforded the acyclic adduct **9**. The reaction of **6a** with 2-aminopyrimidine (**10**) gave the novel unexpected pyrimido[2,1-*d*]1,2,3,5-tetrazine **11**. Acyclic adducts **16** and **17** were obtained from the reaction of **6b** with 2-cyanomethylbenzimidazole (**14**) and 2-aminobenzimidazole (**15**), respectively.

Keywords: Nitrilimines, ethyl pyridine-2-acetate, pyrrolo[1,2-*a*]pyridine, 2-aminopyrimidine, pyrimido[2,1-*d*]1,2,3,5-tetrazine, 2-cyanomethylbenzimidazole, 2-aminobenzimidazole

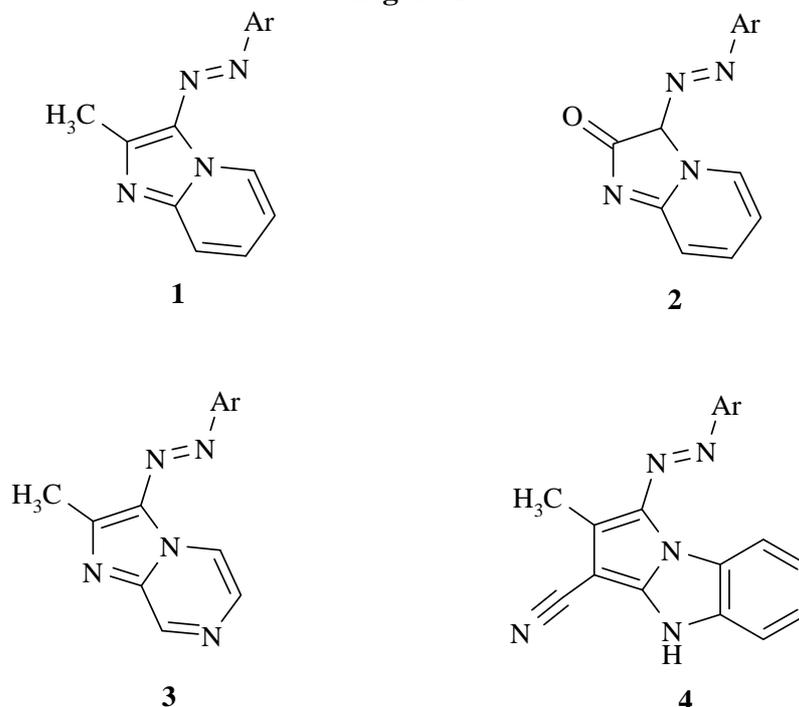
Introduction

Pyrrolo[1,2-*a*]pyridine (inolizine) derivatives possess a wide range of physiological activity, which depend on the nature of the substituents and their position on the molecule. They are used as 5-lipoxygenase pathway inhibitors [1]. Their uses for different purposes, including their interesting

biological activities, were summarized by Wang *et al.* [2]. Recently, Gundersen *et al.* reported the synthesis of indolizine derivatives with selective antibacterial activity against *Mycobacterium tuberculosis* [3]. Indolizine derivatives can be prepared by different routes, including the 1,3-dipolar cycloaddition reaction of pyridyl nitrilimines with dimethyl acetylenedicarboxylate [4]. 1,3-Dipolar cycloadditions of pyridinium *N*-ylides to alkenes were also used for their preparation [2]. Propargyl-substituted pyridine [5] and propargyl amines or amides [6] were recently used for their synthesis.

The synthesis of different fused heterocyclic systems was recently reported using nitrilimines and 2-substituted aza-heterocycles. These include imidazo[1,2-*a*]pyridines **1** [7] and their 2-one derivatives **2** [8], imidazo[1,2-*a*]pyrazines **3** [9] and pyrrolo[1,2-*a*]benzimidazole **4** [10] (Figure 1). The present work describes the synthesis of new indolizine derivatives in good yields *via* a one-pot reaction which utilizes simple conditions and inexpensive reagents.

Figure 1.



The above reactions are examples of a type of reaction in which a dinucleophilic heterocyclic molecule reacts at the two electrophilic centers of nitrilimines, namely, the terminal carbon of the dipole, and the carbonyl carbon of the acetyl or ester moiety attached to that carbon. This work will investigate the reaction of nitrilimines with different similar dinucleophilic heterocycles (ethyl pyridine-2-acetate, 2-aminopyrimidine, 2-cyanomethylbenzimidazole and 2-aminobenzimidazole).

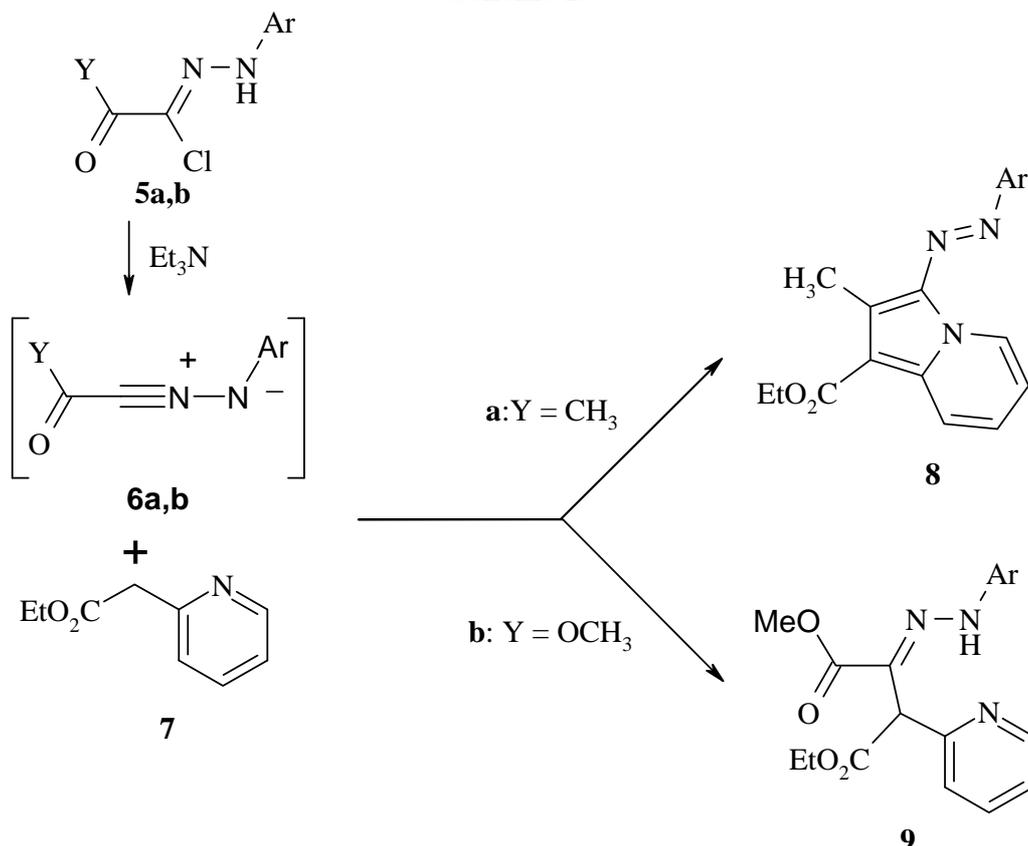
Results and Discussion

Reaction of nitrilimines with ethyl pyridine-2-acetate.

The reaction was carried out by mixing a slight excess of ethyl pyridine-2-acetate (**7**) with hydrazonoyl halides **5** in tetrahydrofuran in the presence of triethylamine (Scheme 1). The reaction

mixture was stirred for 48 hours at room temperature. The products were then separated and identified by their spectral data. Different reaction modes were observed depending on the Y residue of the hydrazonoyl halides. Pyrrolo[1,2-a]pyridine **8** was obtained when Y is CH₃, while the acyclic addition product **9** was obtained when Y is OCH₃. Structure elucidation of both products was based mainly on their NMR spectral data, presented in the Experimental.

Scheme 1.

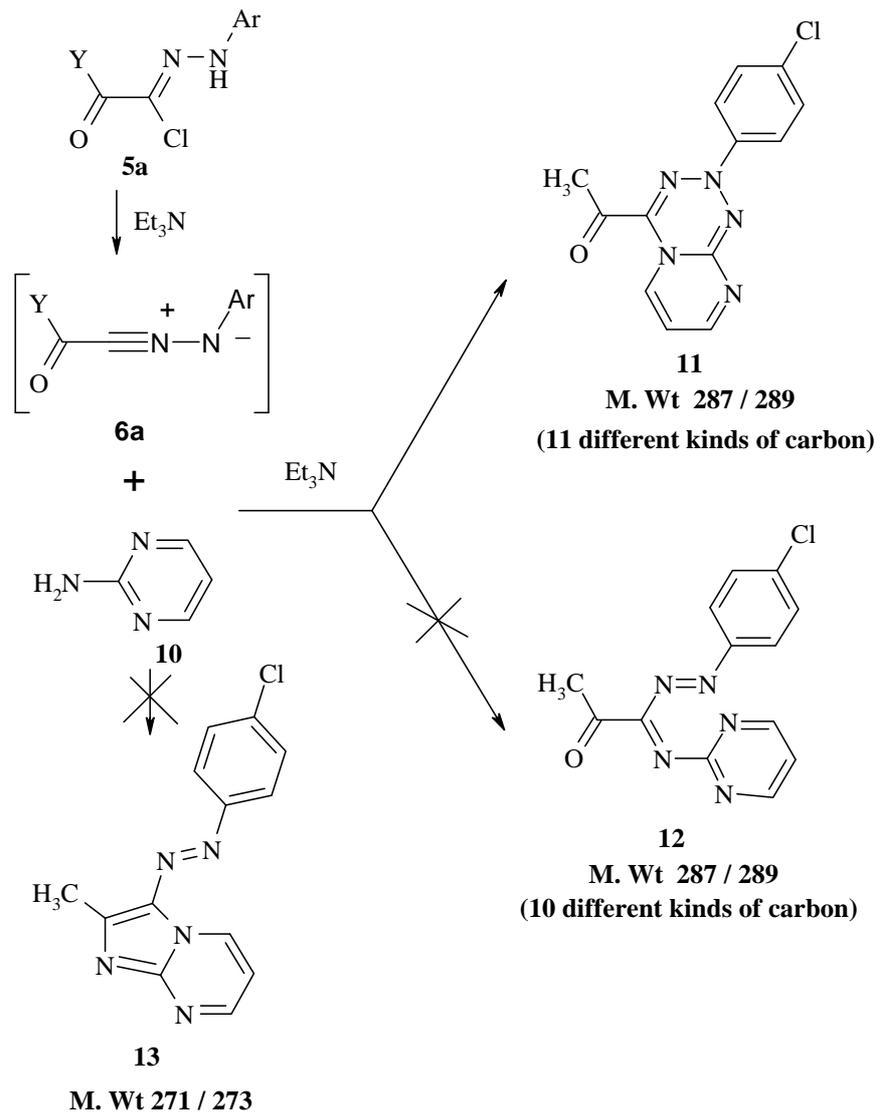


Reaction of nitrilimines with 2-aminopyrimidine

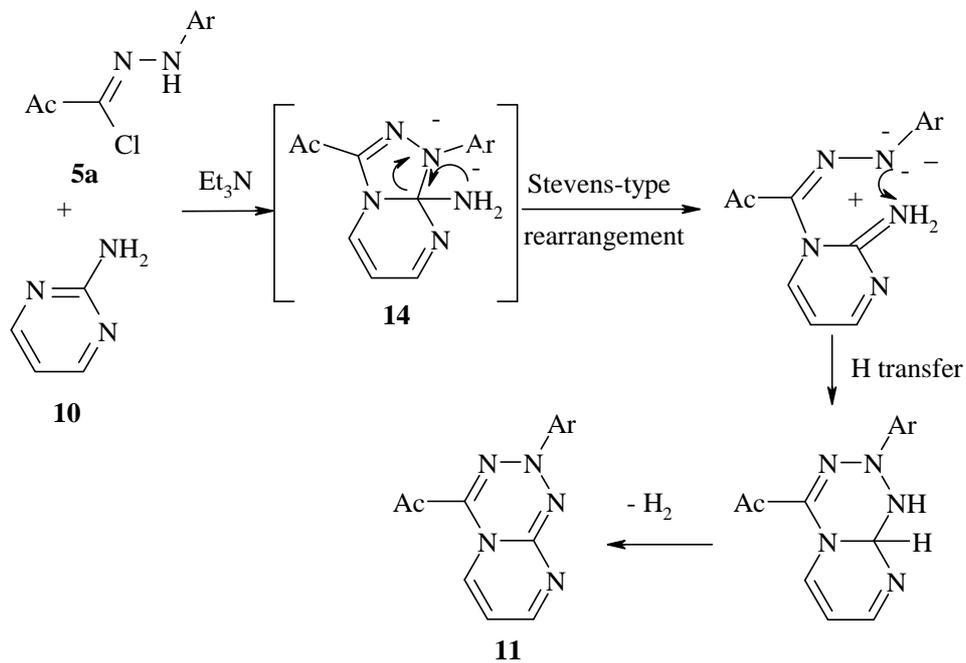
In this case the product was characterized to be the pyrimido[2,1-d]1,2,3,5-tetrazine **11**, rather than the expected products **12** or **13** (Scheme 2). The structure elucidation was based mainly on MS and NMR spectral data of the product. The molecular weight of the product and the presence of a C=O signal in the ¹³C-NMR excludes structure **13**. Eleven signals in the ¹³C-NMR spectrum are in accordance with structure **11** rather than the acyclic structure **12**.

A plausible reaction mechanism for the formation of **11** is depicted in Scheme 3. It is suggested that the reaction starts with the 1,3-dipolar cycloaddition of the nitrilimine with aminopyrimidine producing the intermediate cycloaddition product **14**. The later then recycles to **11** in a Stevens-type rearrangement followed by oxidation.

Scheme 2.



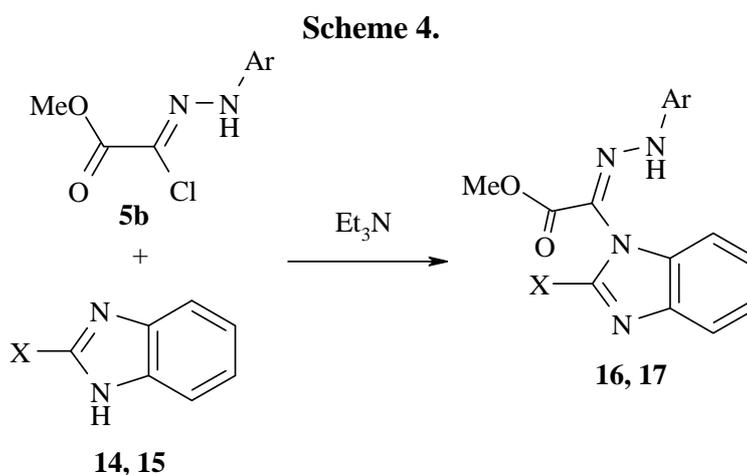
Scheme 3.



Pyrimido[2,1-d]1,2,3,5-tetrazines have not been reported in the literature according to our knowledge. Different pyrimido[1,2-b]1,2,4,5-tetrazines were prepared by reaction of 3-aminopyrimidine with hydrazonoyl halides [11]. The synthesis and biological activity of pyrimido[1,2-b]1,2,4,5-tetrazin-6-one against HCMV protease was described by Grandi *et al.* [12].

Reaction of nitrilimines with 2-cyanomethylbenzimidazole and 2-aminobenzimidazole

This reaction gave nucleophilic addition products **16** and **17**, respectively (Scheme 4). The spectral data are in accordance with the suggested structures.



Experimental

General

Melting points were determined on an Electrothermal Mel. Temp. apparatus and are uncorrected. ¹H- and ¹³C NMR spectra were recorded on a Bruker 300 MHz instrument for solutions in CDCl₃ or DMSO-d₆ at 21 °C, using TMS as an internal reference. Chemical shifts are expressed in δ (ppm) downfield from TMS. EI-MS spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV. The hydrazonoyl chlorides **5a,b** were prepared as previously described [13].

Reaction of nitrilimines **5** with 2-substituted heterocycles **7**, **10**, **14** and **15**

Triethylamine (0.01 mol, 1.4 mL) was added dropwise at room temperature to a mixture of a hydrazonoyl halide **5a,b** (0.01 mol) and the appropriate heterocycle (0.01 mol) in tetrahydrofuran (50 mL). The reaction mixture was stirred for two days. The precipitated salt was filtered off and the solvent was then evaporated. The residual solid was washed twice with water and then triturated with

ethanol. The solid was collected using suction filtration and recrystallized from a suitable solvent. The purity of the compounds was checked using TLC.

The following compounds were prepared applying this procedure:

8-Ethoxycarbonyl-7-methyl-6-(4-chlorophenylazo)pyrrolo[1,2-a]pyridine (8). Yield: 70%, orange solid, m.p. = 128 °C; ¹H-NMR (DMSO-d₆) δ: 1.34 (t, *J*=7.0 Hz, 3H, CH₃), 2.74 (s, 3H, CH₃), 4.3 (q, *J*=7.0 Hz, 2H, OCH₂), 9.9-7.21 (m, 8H, ArC-H); ¹³C-NMR (DMSO-d₆) δ: 12.28 (CH₃), 14.84 (CH₃), 60.11 (OCH₂), 116.73, 116.90, 119.09, 123.25, 129.59, 129.72 (6ArCH), 106.47, 128.42, 129.64, 133.48, 137.87, 152.58 (6ArC), 164.29 (C=O).

Methyl 2-(4-chlorophenylhydrazono)-3-(pyridine-2-yl)-3-ethoxycarbonylpropanoate (9). Yield: 63%, yellow solid, m.p. = 138-139 °C; ¹H-NMR (DMSO-d₆) δ 1.04 (t, *J*=7.0 Hz, 3H, CH₃), 3.76 (s, 3H, OCH₃), 3.86 (q, *J*=7.0 Hz, 2H, OCH₂), 8.16-6.11 (m, 8H, ArC-H), 10.8 (s, 1H, NH); ¹³C-NMR (DMSO-d₆) δ 15.05 (CH₃), 53.22 (OCH₃), 57.93 (OCH₂), 76.64 (CH), 107.88, 116.78, 120.73, 129.64, 134.55, 136.99 (6ArCH), 123.53, 127.00, 142.40, 151.53, (C=N, 3ArC), 161.45 (C=O), 167.52(C=O).

4-Acetyl-2-(4-chlorophenyl)pyrimido[2,1-d]1,2,3,5-tetrazine (11). Yield: 63%, brown solid, m.p. = 191 °C; ¹H-NMR (DMSO-d₆) δ 2.51 (s, 3H, CH₃), 5.51(t, *J*=11.0 Hz, 1H, ArCH), 7.55 (d, *J*=9.0 Hz, 2H, ArCH), 7.93 (d, *J*=9.0 Hz, 2H, ArCH), 7.61 (d, *J*=11.0 Hz, 1H, ArCH), 8.67 (d, *J*=11.0 Hz, 1H, ArCH); ¹³C-NMR (DMSO-d₆) δ 27.29 (CH₃), 132.00, 136.82, 157.62, 161.44, (4ArC), 101.50, 124.95, 129.38, 160.91, 169.39 (5ArCH), 191.66 (C=O); MS: *m/z*: 287/289 (35, M⁺), 271/273 (100), 151/153 (37), 94 (72).

Methyl 2-(4-chlorophenyl)-2-(2-aminobenzimidazol-1-yl)ethanoate (16). Yield: 81%, white solid, m.p. = 198 °C; ¹H-NMR (DMSO-d₆) δ 3.70 (s, 3H, OCH₃), 6.52 (s, 2H, NH₂), 6.65 (d, *J*=7.0 Hz, 1H, ArCH), 6.79 (t, *J*=8.0 Hz, 1H, ArCH), 6.97 (t, *J*=8.0 Hz, 1H, ArCH), 7.16 (d, *J*=7.0 Hz, 1H, ArCH), 7.33 (s, 4H, 4-ClC₆H₄); ¹³C-NMR (DMSO-d₆) δ 52.80 (OCH₃), 108.08, 115.52, 116.72, 119.13, 121.96, 129.47 (6ArCH), 119.85, 126.51, 133.89, 142.60, 144.55, 155.00 (C=N + 5ArC), 161.75 (C=O).

Methyl 2-(4-chlorophenyl)-2-(2-cyanomethylbenzimidazol-1-yl)ethanoate (17). Yield: 77%, pale yellow solid, m.p. = 206 °C; ¹H-NMR (DMSO-d₆) δ 3.74 (s, 3H, OCH₃), 4.25 (2d(AB system), 2H, CH₂), 7.12 (d, *J*=7.0 Hz, 1H, ArCH), 7.37-7.23 (m, 6H, ArCH), 7.74 (d, *J*=7.0 Hz, 1H, ArCH), 10.97 (s, 1H, NH), ¹³C-NMR (DMSO-d₆) δ 18.27 (CH₂), 53.20 (OCH₃), 110.74, 117.05, 119.97, 123.45, 124.30, 29.55 (6ArCH), 115.99, 118.21, 127.22, 135.03, 142.23, 142.96, 146.18 (C=N, C≡N, 5ArC), 161.64 (C=O).

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Sample Availability: Contact the authors.