Synthesis of Heteroaryl Substituted Imidazole Derivatives

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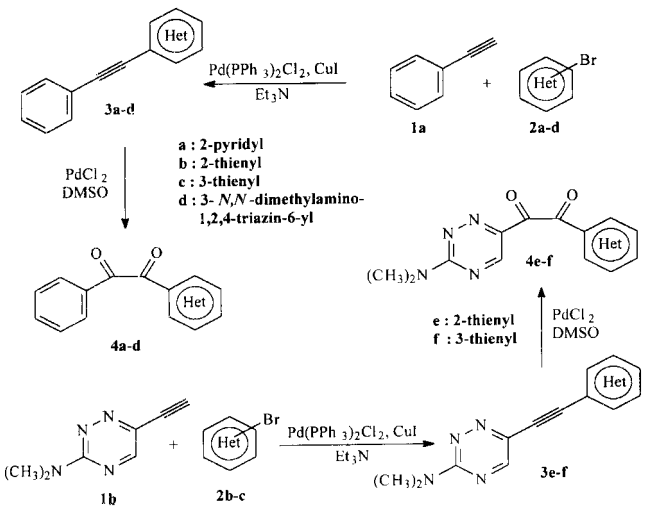
Aryl substituted imidazole derivatives possess valuable pharmacological and agricultural activities such as non-steroidal antiinflammatory drug,[1] fungicide,[2] and cyclooxygenase-2 inhibitor.[3] Recently, appropriated heteroaryl substituted imidazole derivatives were reported to show good antibacterial activity for MRSA.[4] Useful synthetic methods for imidazole derivatives were known to include several intermediates such as α-hydroxy ketones,[5] α-hydroxyimino ketones,[6] or 1,2-diketones.[7] But there are not many heteroaryl substituted imidazole derivatives reported, since efficient methods for preparing the heteroaryl substituted intermediates mentioned above are limitted. In previous paper,[8] we reported the successful transformation of heteroaryl substituted internal acetylene group to 1,2-diketones, and the synthesis of several 1,2,4-triazine dimers. As an extention of this, we like to report the synthesis of heteroaryl substituted imidazole derivatives, including the 1,2,4-triazine substituted imidazole derivatives.



Scheme 1

The coupling reaction of phenylacetylene (**1a**) with 2-bromopyridine (**2a**) was carried out under $Pd(PPh_3)_2Cl_2$ in acetonitrile at 40 °C to give 1-phenyl-2-(2-pyridyl)acetylene (**3a**) with 65% yield. Similarly, the coupling reaction of phenylacetylene with 2-bromothiophene (**2b**) and 6-bromo-3-*N,N*-dimethylamino-1,2,4-triazine (**2d**) were also successfully achieved under the same reaction condition to give 1-phenyl-2-(2-thienyl)acetylene (**3b**) with 68% yield and 1-phenyl-2-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)acetylene (**3d**) with 60% yield respectively. But, 3-bromothiophene (**2c**) was coupled in DMF, not acetonitrile at 100 °C to give 1-phenyl-2-(3-thienyl)acetylene (**3c**) with 55% yield.

Also, 6-ethynyl-3-*N,N*-dimethylamino-1,2,4-triazine (**1b**) was coupled with 2-bromothiophene (**2b**) and 3-bromothiophene (**2c**) to give 1-(2-thienyl)-2-(3-*N,N*-dimethyl-amino-1,2,4-triazin-6-yl)acetylene (**3e**) with 40% yield and 1-(3-thienyl)-2-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)acetylene (**3f**) with 28% yield respcetively. The yields here were rather low, but we did not try to optimize the reaction conditions to increase the yields (Scheme 1).

The oxidation of compounds **3a-d** using $KMnO_4$, NBS/DMSO, and I_2/DMSO were unsuccessful. But the oxidation using $PdCl_2$/DMSO produced successfully 1,2-diketone compounds **4a-d** with low to moderate yield. The yield of compound **4a** was so low, for some reason that we gave up to proceed further reaction.

The cyclization of 1,2-diketone compounds **4b-d** with benzaldehyde and NH_4OAc in acetic acid gave 2,5-diphenyl-4-heteroarylimidazoles **5a-c** with moderate yields. Similarly 2-trifluoromethyl-4,5-diarylimidazoles **6a-c** were synthesized using trifluoroacetaldehyde ethyl hemiacetal and NH_4OAc with 1,2-diketone compounds **4d-f** with low yields (Scheme 2). All the products were identified by the spectral methods, which are reported in Table 1-6.

Table 1. Physical and spectral properties of compounds **3a-e**

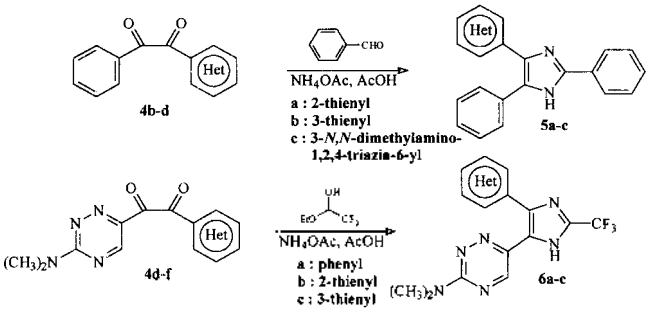
Compound	Heteroaryl	Yield (%)	mp (°C)	^{1}H NMR ($CDCl_3$), δ (ppm)		Ms (m/z, rel. intensity)
				Phenyl	Heteroaryl	
3a	2-pyridyl	65	28-30	7.36 (m)	7.20-7.25 (m), 7.50 (dd)	179(M^+, 100)
				7.59 (m)	7.64 (dd), 8.61 (dd)	151(12)
3b	2-thienyl	68	41-43	7.34 (m)	7.01 (t), 7.28 (m)	184 (M^+, 100)
				7.51 (m)		152 (18)
3c	3-thienyl	55	42-44	7.33 (m)	7.20 (d), 7.30 (t), 7.52 (m)	184 (M^+, 100)
				7.52 (m)		152 (13)
3d	1,2,4-triazin-6-yl	66	152-154	7.25 (m)	3.32 (s, 6H, $N(CH_3)_2$)	224 (M^+, 10)
				7.64 (m)	8.25 (s, 1H, 5-H)	126 (100)

Table 2. Physical and spectral properties of compounds **3e-f**

Compound	Hetero-aryl	Yield (%)	mp (°C)	^{1}H NMR ($CDCl_3$), δ (ppm)		Ms (m/z, rel. intensity)
				1,2,4-triazine	hetero-aryl	
3e	2-thienyl	40	135-137	3.32 (s)	7.04 (t)	230 (M^+, 20)
				8.23 (s)	7.37 (m)	132 (100)
3f	3-thienyl	28	164-166	3.31 (s)	7.38 (dd)	230 (M^+, 25)
				8.23 (s)	7.62 (dd)	132 (100)
					8.14 (d)	

Table 3. Physical and spectral properties of compounds **4a-d**

Compound	Hetero-aryl	Yield (%)	mp (°C)	^{1}H NMR ($CDCl_3$), δ (ppm)		Ms (m/z, rel. intensity)
				phenyl	heteroaryl	
4a	2-pyridyl	10	63-65	7.52 (m)	7.64 (t), 7.97 (m)	211 (M^+, 28)
				7.93 (m)	8.22 (d), 8.67 (dd)	93 (100)
4b	2-thienyl	45	58-60	7.54 (t)	7.19 (t),	216 (M^+, 9)
				7.67 (t)	7.80-7.85 (m)	105 (100)
				8.05 (d)		
4c	3-thienyl	57	36-38	7.51 (t)	7.40 (d), 7.66 (m)	216 (M^+, 7)
				7.63 (m)	8.22 (m)	105 (100)
				8.01 (d)		
4d	1,2,4-tri-azin-6-yl	60	102-104	7.25 (m)	3.30 (s, 6H, $N(CH_3)_2$)	256 (M^+, 22)
				7.74 (m)	8.84 (s, 1H, 5-H)	105 (100)

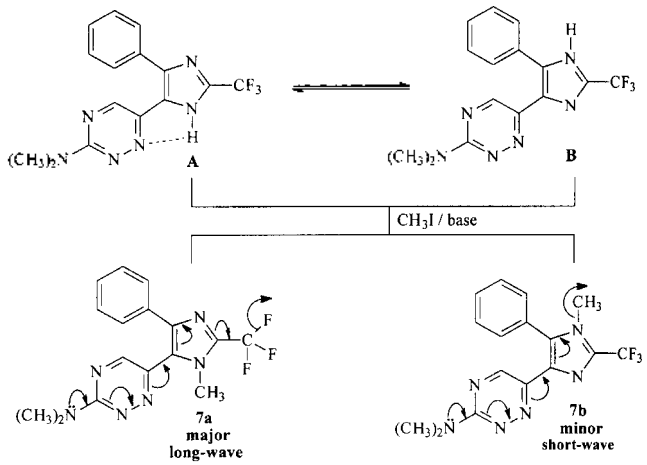


Scheme 2

Since all imidazole derivatives are unsymmetrical, two different tautomers **A** and **B** are possible. In order to clarify which tautomer would be the major one, compound **6a** was selected as a representative, and methylated with methyl iodide under basic condition. Two different products, **7a** and **7b** were obtained as expected. The **7a** would be the model compound for tautomer **A**, and **7b** would be the model compound for tautomer **B**. One had chemical shift of *N*-methyl group at 3.87 for ^{1}H, and 32.76 for ^{13}C NMR and the other had at 3.60 for ^{1}H, and 32.02 for ^{13}C NMR. The one which had down field chemical shift had longer conjugation than the other one which had up field chemical shift (Scheme 3).

Table 4. Physical and spectral properties of compounds **4e-f**

Compound	Hetero-aryl	Yield (%)	mp (°C)	^{1}H NMR ($CDCl_3$), δ (ppm)		Ms (m/z, rel. intensity)
				1,2,4-triazine	heteroaryl	
4e	2-thienyl	45	107-109	3.31 (s, 3H, N-CH_3)	7.17 (t)	262 (M^+, 39)
				3.46 (s, 3H, N-CH_3)	7.71 (d)	53 (100)
				8.83 (s, 1H, 5-H)	7.82 (d)	
4f	3-thienyl	30	105-107	3.31 (s, 3H, N-CH_3)	7.38 (dd)	262 (M^+, 39)
				3.47 (s, 3H, N-CH_3)	7.64 (dd)	111 (100)
				8.83 (s, 1H, 5-H)	8.13 (s)	



Scheme 3

Table 5. Physical and spectral properties of compounds **5a-c**

Compound	Hetero-aryl	Yield (%)	mp (°C)	^{1}H NMR ($CDCl_3$), δ (ppm)		Ms (m/z, rel. intensity)
				Phenyl	Heteroaryl	
5a	2-thienyl	50	232-234	7.36-7.46 (m)	6.98 (t),	302 (M^+, 100)
				7.61 (dd)	7.19 (d),	198 (9)
				7.90 (dd)	7.25 (dd)	
5b	3-thienyl	66	236-238	7.35-7.44 (m)	7.21 (d)	302 (M^+, 100)
				7.58 (d)	7.29 (d),	269 (8)
				7.89 (d)	7.31 (d)	
5c	1,2,4-tri-azin-6-yl	55	154-156	7.36-7.46 (m)	3.27 (s),	344 (M^+, 98)
				7.64 (d)	8.35 (s)	244 (100)
				7.95 (d)		

The UV-VIS spectra of the former had longer wave absorption than the latter (see Figure 1 and Table 7).

According to these UV-VIS spectra, we assigned that the methylated compound which had down field chemical shift and longer wavelength absorption was **7a** and the other one was **7b**. By comparing UV-VIS spectra of compound **6a** with the *N*-methylated **7a** and **7b**, which could be used as model compounds for the tautomer **A** and **B**, we could assign that the major tautomer of compd **6a** in solution was **A**. This method comparing the UV-VIS spectra of the tautomeric mixture with that of their model compounds to assign the tautomeric equilibrium is well known.[9,10]

The antibacterial activities of compound **5a-c** and **6a-c** were tested on *G. Cingulata*, *C. Miyabeanus* and *R. Solani*,[11] and showed no particular activities.

In conclusion, we could synthesize the various heteroaryl substituted imidazole derivatives through the reaction of Pd catalyzed coupling of acetylene to heteroaromatic compounds and decided the tautomeric behavior of 4-phenyl-5-(3-*N*,*N*-dimethylamino-1,2,4-triazin-6-yl)-2-trifluoromethylimidazole in solution.

Table 6. Physical and spectral properties of compounds **6a-c**

Compound	Heteroaryl	Yield (%)	mp (°C)	^{1}H NMR($CDCl_3$), (ppm)		Ms (m/z, rel. intensity)
				1,2,4-triazine	heteroaryl	
6a	phenyl	55	154-156	3.28 (s, 6H, $N(CH_3)_2$)	7.42 (m), 7.56 (m)	334 (M^+, 48)
				8.27 (s, 1H, 5-H)	11.16 (br)	217 (100)
6b	2-thienyl	30	173-175	3.20 (s, 3H, N-CH_3)	6.92 (t), 7.27 (d)	341 (M^+, 48)
				3.47 (s, 3H, N-CH_3)	7.32 (d), 11.93 (br)	222 (100)
				9.13 (s, 1H, 5-H)		
6c	3-thienyl	25	200-202	3.24 (s, 6H, $N(CH_3)_2$)	7.33(d), 7.56 (d)	341 (M^+, 48)
				8.76 (s, 1H, 5-H)	8.07 (s)	222 (100)

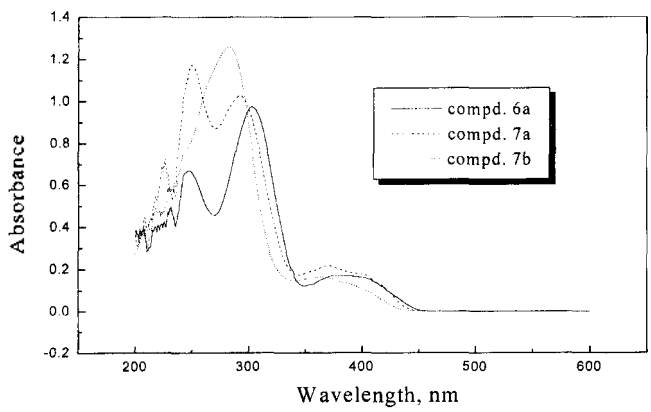


Figure 1. UV-VIS spectra of compounds **6a**, **7a** and **7b** in $CHCl_3$ (10^{-4} M).

Experimental Section

All chemicals were purchased from Aldrich, and used without further purification. NMR and mass spectra were recorded on Varian EM-360, General Electric QE-300 and Shimazu GC MS-QP-1000A, respectively. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected.

2,5-Diphenyl-4-(2-thienyl)imidazole (5a) (General procedure for the condensation of 1,2-diketones with aldehyde). To a solution of 1-phenyl-2-(2-thienyl)ethandione (0.22 g, 1.0 mmol) **4b** and ammonium acetate (0.70 g, 9.0 mmol) in acetic acid (10 mL) was slowly added benzaldehyde (0.21 g, 2.0 mmol). After refluxed for 3 hrs, the mixture was poured into ice-water (25 mL), and then extracted with ethyl ether. The organic solvent was washed with aqueous sodium bicarbonate solution and removed under reduced pressure. The residue was purified by silica gel column chromatography using *n*-hexane, ethyl acetate and benzene (3 : 5 : 7) to give product **5a** as yellow solid.

***N*-Methyl-4-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-5-phenyl-2-trifluoromethylimidzole (7a) and *N*-methyl-4-phenyl-5-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-2-tri- fluoromethylimidazole (7b)**. To a solution of 2-trifluoromethyl-4-phenyl-5-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)imidazole **6a** (0.40 g, 1.3 mmol) in DMF (10 mL) was slowly added anhydrous K_2CO_3 (0.28 g, 2.0 mmol) and methyl iodide (0.74 g, 5.2 mmol). After stirred for 3 hrs at 70 °C, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using *n*-hexane, ethyl acetate and benzene (10 : 3 : 2) to give product **7** as yellow solid. major **7a**: 45%, mp 114-116 °C, ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 6H, $(NCH_3)_2$), 3.88 (s, 3H, N-CH_3), 7.29-7.46 (m, 5H, Ph), 7.94 (s, 1H, Tri-H); Mass: m/e (rel. intensity), 348 (M^+, 30), 251 (100). minor **7b**: 35%, mp 174-176 °C, ^{1}H NMR ($CDCl_3$) δ 3.22 (s, 6H, $(NCH_3)_2$), 3.60 (s, 3H, N-CH_3), 7.41-7.49 (m, 5H, Ph), 8.56 (s, 1H, Tri-H); Mass: m/e (rel. intensity), 348 (M^+, 16), 251 (100).

Table 7. UV-VIS data of compound **6a**, **7a** and **7b**

Compound	λ_{max}/nm (ε)	λ_{max}/nm (ε)	λ_{max}/nm (ε)
6a	372 (3300)	301 (18680)	252 (14600)
7a	370 (3300)	291 (16000)	250 (19300)
7b	370 (2600)	282 (21000)	

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