

FACILE SYNTHESIS OF IMIDAZO[2,1-c][1,2,4] TRIAZOLONES DERIVATIVES

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Abstract : α -bromoesters and oxalyl chloride react with 5-amino-1-phenyl-1,2,4-triazoles to give in anhydrous conditions and with good yields, imidazo [2,1-c][1,2,4] triazolones.

Keywords : 5-amino-1-phenyl-1,2,4-triazoles, imidazotriazolones

Introduction

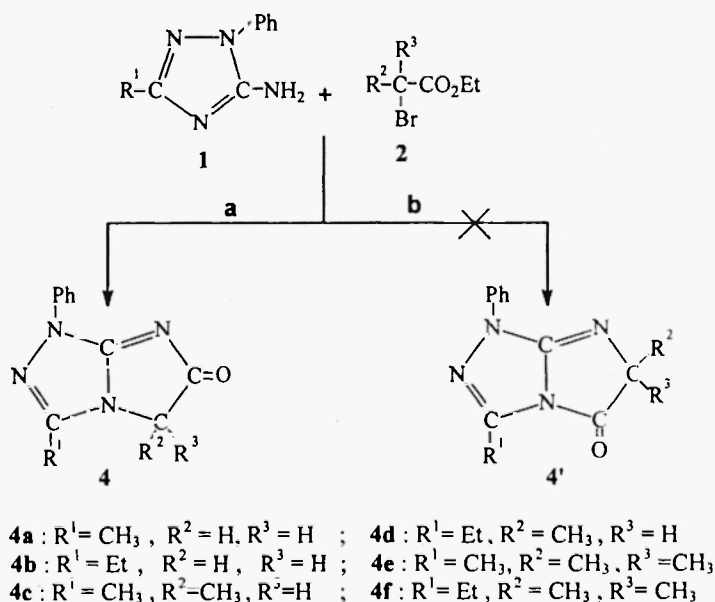
A number of studies have been carried out on the reaction of aminotriazoles with bielelectrophiles compounds giving a bicyclic heterocycles (1-8). Many compounds of this group have a great interest thanks to their potential biological and pharmacological activities (9-10). In this present work we report a method for obtaining a new class of imidazo [2,1-c][1,2,4] triazolones 4 and 5 as a result of the cyclocondensation of 5-amino-1-phenyl -1, 2, 4 - triazoles 1 with α -bromoesters 2 and with oxalyl chloride 3 , respectively.

Results and discussion

The α -bromoesters and oxalyl chloride have two electrophilic sites for attack by nucléophilic reagents, such as 5-amino-1-phenyl-1,2,4-triazoles , to produce biheterocyclic compounds.

Synthesis of imidazo[2,1-c][1,2,4]triazol-6-ones

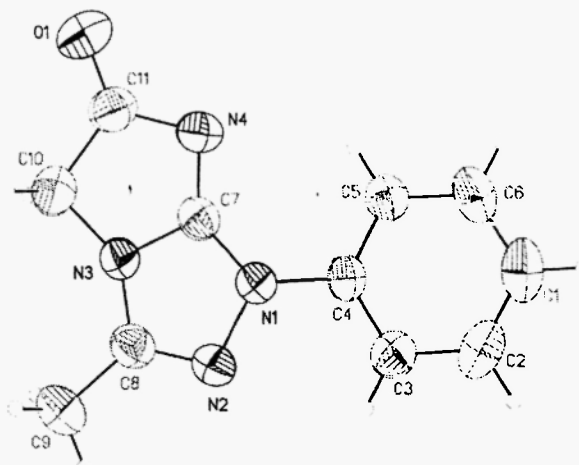
The reaction of amino triazole 1 with α -bromoesters 2 in the presence of sodium hydride gave a series of imidazotriazolones wich would have the structures 4 or their isomers 4' (scheme 1).



Scheme I.

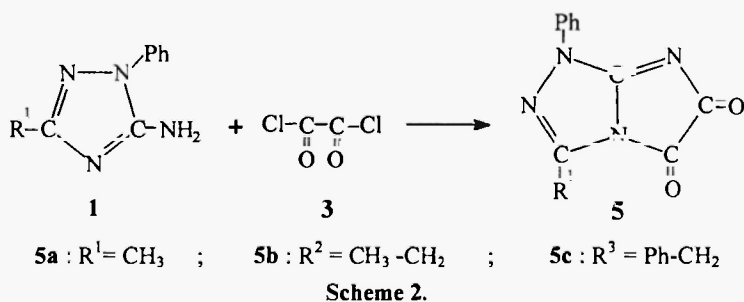
The structure elucidation was achieved by X-ray analysis, and proved that we obtained only the imidazo [2,1-c][1,2,4]triazol-6-ones **4**. The structures of the compounds prepared were confirmed by, NMR, IR and mass spectroscopy.

Figure 1. X-Ray structure of **4a**



Synthesis of imidazo[2,1-c][1,2,4]triazol-5-6-diones

The addition, in cool conditions and in the presence of slight excess of pyridine, oxalyl chlorides **3** react with 1-phenyl-5-amino-1,2,4-triazoles to produce with good yield the corresponding imidazo [2,1-c][1,2,4] triazol-5-6-diones **5**.



The structures of compounds **5** have been assigned from their analytical data, elemental analysis, IR, NMR, and mass spectroscopy. In fact, the IR spectra also revealed the absence of absorbance due to the NH band. The mass spectra showed essentially the molecular peak (M^+).

Conclusion

In conclusion, we present an efficient method for the preparation of a new class of imidazotriazolones **4** and **5** from the 5-amino-1-phenyl-1,2,4-triazoles **1**. The condensation of this last with others bielectrophilic reagents is actually under progress.

Experimental

NMR spectra were recorded on a Bruker AC 300 (^1H at 300 MHz, ^{13}C at 75 MHz) in CDCl_3 for compounds **4** and DMSO- d_6 for **5**. All chemical shifts are recorded in parts per million (ppm) downfield from tetramethylsilane. Coupling constants (3J) are given in Hertz (Hz). IR spectra were determined for KBr discs on a JASCO FT-IR-420

spectrometer. The mass spectra were measured using an AEI MS-50 mass spectrometer operating in electron impact mode at 70 eV.

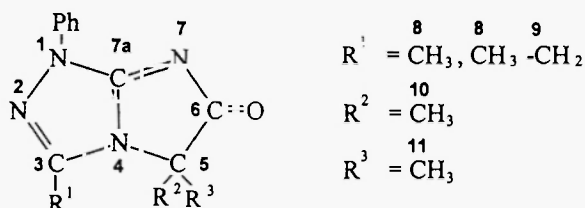
Melting point: the melting points were determined in Electrothermal 9100 apparatus and are uncorrected.

The reactions were monitored by thin layer chromatography (TLC) using aluminium sheets with silica gel 60 F₂₅₄ (Merck).

The 5-amino-1-phenyl-1,2,4-triazoles have been prepared following the similar method to that presented in the literature(11).

General Procedure for the Synthesis of imidazo [2,1-c][1,2,4] triazol-6-ones 4a-f

A solution of the 5-amino-1-phenyl-1,2,4-triazole **1** (1mmol) in THF(20ml) was added dropwise over 30 min to a suspension of NaH (2mmol) in THF (20ml) at 0°C. A solution of the α -bromoester **2** (1.2 mmol) in THF (20ml) was then added dropwise. The reaction was stirred at room temperature for 5h. The solvent was removed by rotary evaporation and the residue was taken up in CHCl₃ (60ml), washed with water (2X20ml), and dried over MgSO₄. The solvent was removed under vacuum and the product was purified by column chromatography using CHCl₃/CH₃OH 99:1



3-methyl-1-phenyl-1H-imidazo[2,1-c][1,2,4]triazol-6-one (4a)

Yield = 69%; Mp=247°C; IR : ν C=O : 1738 cm⁻¹, ν C=N : 1624 cm⁻¹; ¹H NMR : 2.43(s, 3H) ; 4.31(s, 2H) ; 7.26-8.00(mu, 5H) ; ¹³C NMR : C₈ 11.44 ; C₅ 50.03; C_{arom} 118.72-136.34; C₃ 144.66; C_{7a} 165.37; C₆=185.22 ; Mass m/z (%) : 214 (M⁺, 33); 145 (100); 117(15); 91 (20); 77 (80); 42(78).

3-ethyl-1-phenyl -1H-imidazo[2,1-c][1,2,4]triazol-6-one (4b)

Yield = 65%; Mp= 241°C; IR: ν C=O : 1710 cm⁻¹, ν C=N : 1619 cm⁻¹; ¹H NMR : 1.25(t, ³J_{HH}= 7.5, 3H); 2.65(q, ³J_{HH}= 7.5, 2H); 4.17(s, 2H); 7.27-8.00(mu, 5H); ¹³C NMR : C₈ 12.7; C₉ 22.1; C₅=48.8; C_{arom} 118.7-136.9; C₃ 154.5; C_{7a} 163.2; C₆ 184.2; Mass m/z (%):228 (M⁺, 41); 145 (100); 117(15); 91 (20); 77 (80); 42(78).

3,5-dimethyl-1-phenyl -1H-imidazo[2,1-c][1,2,4]triazol-6-one (4c)

Yield = 74%; Mp=162°C; IR : ν C=O : 1715 cm⁻¹, ν C=N : 1602 cm⁻¹ ; ¹H NMR : 1.68(d, ³J_{HH}= 7.2, 3H); 2.44(s, 3H); 4.41(q, ³J_{HH}= 7.2, 1H); 7.26-8.02(mu, 5H); ¹³C NMR : C₈ 11.5; C₁₀ 15.9; C₅ 58.8; C_{arom} 119.0-136.7; C₃ 144.9 ; C_{7a} 164.6; C₆ 189.1; Mass m/z (%) : 228 (M⁺, 100); 200(60); 145 (90); 117(15); 91 (50); 77 (84); 42(34).

3-ethyl-5-methyl-1-phenyl -1H- [2,1-c][1,2,4]triazol-6-one(4d)

Yield = 68%; Mp=165°C; IR : ν C=O : 1719 cm⁻¹, ν C=N : 1596 cm⁻¹ ; ¹H NMR : 1.41(t, ³J_{HH}= 7.5, 3H); 1.67(d, ³J_{HH}= 7.2, 3H); 2.75(q, ³J_{HH}= 7.5, 2H); 4.39 (q, ³J_{HH}= 7.2, 1H); 7.24-8.03 (mu, 5H) ; ¹³C NMR : C₈ 10.2; C₁₀ 15.8; C₉ 19.2; C₅ 58.5; C_{arom} 118.7-136.4 ; C₃ 149.1; C_{7a} 164.3; C₆ 188.8; Mass m/z (%) : 242 (M⁺, 100); 213(60) ; 145 (50); 117(10); 91 (30); 77 (49); 42(9).

3,5,5-trimethyl-1-phenyl-1H-imidazo[2,1-c][1,2,4]triazol-6-one(4e)

Yield = 59%; Mp= 139°C; IR: ν C=O : 1710 cm⁻¹, ν C=N : 1635 cm⁻¹; ¹H NMR : 1.93(s, 6H); 2.45(s, 3H); 7.27-7.70(mu, 5H); ¹³C NMR : C₈ 13.6; C₁₀ 31.4 ; C₁₁ 31.4; C₅ 60.6 ; C_{arom} 122.5-136.8; C₃ 148.41; C_{7a} 162.31; C₆ 187.72; Mass m/z (%) : 242 (M⁺, 11); 215(30) ; 188 (12); 91 (27); 77 (27); 43(100).

3-ethyl-5,5-dimethyl-1-phenyl -1H-imidazo [2,1-c][1,2,4]triazol-6-one(4f)

Yield = 57%; Mp= 118°C; IR: ν C=O : 1706 cm⁻¹, ν C=N : 1600 cm⁻¹ ; ¹H NMR : 1.36(t, ³J_{HH}= 7.5, 3H); 1.96(s, 6H); 2.79(q, ³J_{HH}= 7.5, 2H); 7.26-7.50(mu, 5H); ¹³C NMR : C₈ 11.69; C₉ 20.2; C₁₀ 32.1; C₁₁ 32.1; C₅ 60.1; C_{arom} 122.4-137.3; C₃ 149.16; C_{7a} 163.31; C₆ 188.15; Mass m/z (%) : 256 (M⁺, 10); 215(30) ; 188 (12); 91 (27); 77 (27); 43(100).

General Procedure for the Synthesis of imidazo [2,1-c][1,2,4] triazol-5,6-diones 5a-c

Pyridine (2mmol)in methylene chloride(20ml) was added to a solution of 5-amino-1-phenyl-1,2,4-triazole **1** (1mmol) in methylene chloride (20ml) and the mixture was stirred for 10min. Oxalyl chloride **3** (1.1mmol) in

methylene chloride (20ml) was added over a period of 30min, and the reaction was stirred for 4h at room temperature. The reaction was washed with 1M HCl (2X20ml) and water (2X20ml). The aqueous layer was extracted with methylene chloride, the combined organic layer were dried over MgSO_4 . The solvent was removed under vacuum, and the product was purified by recrystallisation in methanol.

3-methyl-1-phenyl-1H-imidazo[2,1-c][1,2,4]triazol-5,6-dione (5a)

Yield = 74%; Mp=194°C; IR : $\nu_{\text{C=O}}$: 1719 cm^{-1} , $\nu_{\text{C=N}}$: 1598 cm^{-1} ; ^1H NMR: 2.49(s, 3H); 7.26-7.48(mu, 5H); Mass m/z (%): 228(M^+ , 13); 117 (28); 91 (53); 77 (100); 43(78); Calculated for $\text{C}_{11}\text{H}_8\text{N}_4\text{O}_2$: %C 57.89; %H 3.53; %N 24.55. Found %C 58.15; %H 3.78; %N 24.72.

3-ethyl-1-phenyl-1H-imidazo[2,1-c][1,2,4]triazol-5,6-dione (5b)

Yield = 72%; Mp=191°C; IR : $\nu_{\text{C=O}}$: 1714 cm^{-1} , $\nu_{\text{C=N}}$: 1602 cm^{-1} ; ^1H NMR: 1.25(t, $^3J_{\text{HH}} = 7.5$, 3H); 2.65(q, $^3J_{\text{HH}} = 7.5$, 2H); 7.27-7.50(mu, 5H); Mass m/z (%): 242 (M^+ , 11); 117 (28); 91 (53); 77 (100); 43(78). Calculated for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_2$: %C 59.50; %H 4.16; %N 23.12. Found %C 59.76; %H 4.44; %N 23.25.

3-benzyl-1-phenyl-1H-imidazo[2,1-c][1,2,4]triazol-5,6-dione (5c)

Yield = 72%; Mp=109°C; IR : $\nu_{\text{C=O}}$: 1717 cm^{-1} , $\nu_{\text{C=N}}$: 1596 cm^{-1} ; ^1H NMR: 4.00(s, 2H); 7.14-7.44(mu, 10H); Mass m/z (%): 303 (M^+ , 9); 117 (20); 91 (60); 77 (90); 43(100). Calculated for $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2$: %C 67.10; %H 3.97; %N 18.41. Found %C 67.33; %H 4.15; %N 18.32.

Crystal data for 4a : $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}$. M=214.23; monoclinic crystal system, space group $\text{P2}_1/\text{c}$, $a=7.2001(2)$, $b=10.9071(3)$, $c=13.2681(4)$ Å, $\beta=103.0320(10)^\circ$, $V=1015.14(5)$ Å³, $Z=4$, $d_{\text{calc}}=1.402$, $T=293(2)$, $R_1=0.0461$, $wR_2=0.1206$ for 2293 independent reflexions with $I>2\sigma(I)$ and $\text{GOOF}=0.963$.

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