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

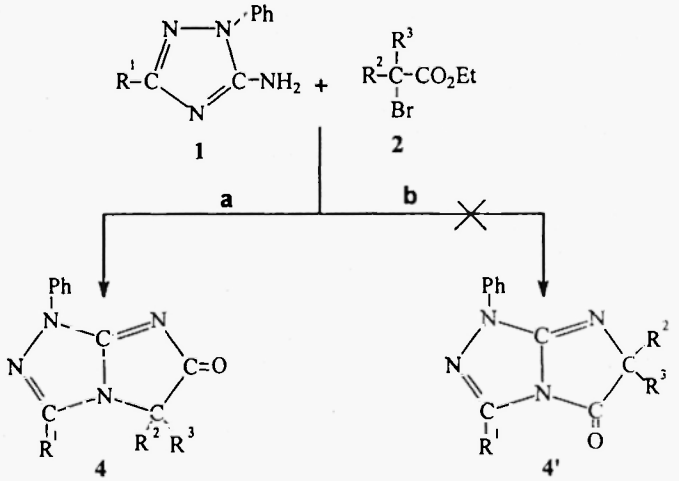
A number of studies have been carried out on the reaction of aminotriazoles with bielectrophiles compounds giving a bicyclic heterocycles (1-8). Many compounds of this group have a great interest thanks to their potential biological and pharmacological activities (9-10). In this present work we report 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 nucleophilic 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).

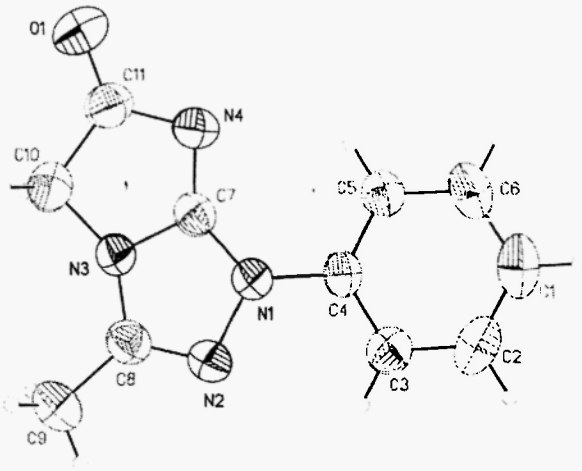


4a : $R^1 = CH_3$, $R^2 = H$, $R^3 = H$; **4d** : $R^1 = Et$, $R^2 = CH_3$, $R^3 = H$
4b : $R^1 = Et$, $R^2 = H$, $R^3 = H$; **4e** : $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = CH_3$
4c : $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$; **4f** : $R^1 = Et$, $R^2 = CH_3$, $R^3 = CH_3$

Scheme I.

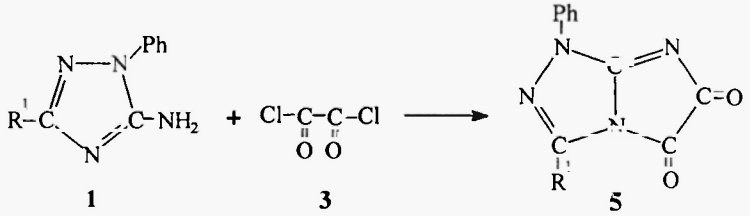
The structure elucidation was achieved by X-ray analysis, and proved that we obtained only the imidazo [2,1-c][1,2,4]triazol-6-ones **4**. The structures of the compounds prepared were confirmed by, NMR, IR and mass spectroscopy.

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 yied the corresponding imidazo [2,1-c][1,2,4] triazol-5-6-diones **5**.



1 **3** **5**

5a : $R^1 = CH_3$; **5b** : $R^2 = CH_3\text{-}CH_2$; **5c** : $R^3 = Ph\text{-}CH_2$

Scheme 2.

The structures of compounds **5** have been assingned 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 ($M^{+\cdot}$).

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.

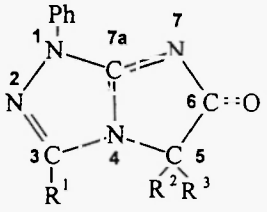
Experimental

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 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 F_{254} (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 $CHCl_3$ (60ml), washed with water (2X20ml), and dried over $MgSO_4$. The solvent was removed under vacuum and the product was purified by column chromatography using $CHCl_3/CH_3OH$ 99:1



R^1 = CH_3 (8), CH_3 (8), $-CH_2$ (9)
R^2 = CH_3 (10)
R^3 = CH_3 (11)

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

Yield= 69%; Mp=247°C; IR : νC=O : 1738 cm^{-1} ,νC=N : 1624 cm^{-1}; ^{1}H NMR : 2.43(s, 3H) ; 4.31(s, 2H) ; 7.26-8.00(mu, 5H) ; ^{13}C NMR : C_8 11.44 ; C_5 50.03; C_{arom} 118.72-136.34; C_3 144.66; C_{7a} 165.37; C_6=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: νC=O : 1710 cm^{-1} ,νC=N : 1619 cm^{-1}; ^{1}H 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); ^{13}C NMR : C_8 12.7; C_9 22.1; C_5=48.8; C_{arom} 118.7-136.9; C_3 154.5; C_{7a} 163.2; C_6 184.2; 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 : νC=O : 1715 cm^{-1} ,νC=N : 1602 cm^{-1} ; ^{1}H 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); ^{13}C NMR : C_8 11.5; C_{10} 15.9; C_5 58.8; C_{arom} 119.0-136.7; C_3 144.9 ; C_{7a} 164.6; C_6 189.1; 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 : νC=O : 1719 cm^{-1} ,νC=N : 1596 cm^{-1}; ^{1}H 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) ; ^{13}C NMR :C_8 10.2; C_{10} 15.8; C_9 19.2; C_5 58.5; C_{arom} 118.7-136.4 ; C_3 149.1; C_{7a} 164.3; C_6 188.8; 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: νC=O : 1710 cm^{-1} ,νC=N : 1635 cm^{-1}; ^{1}H NMR : 1.93(s, 6H); 2.45(s, 3H); 7.27-7.70(mu, 5H); ^{13}C NMR : C_8 13.6; C_{10} 31.4 ; C_{11} 31.4; C_5 60.6 ; C_{arom} 122.5-136.8; C_3 148.41; C_{7a} 162.31; C_6 187.72; 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: νC=O : 1706 cm^{-1} ,νC=N : 1600 cm^{-1}; ^{1}H 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); ^{13}C NMR : C_8 11.69; C_9 20.2; C_{10} 32.1; C_{11} 32.1; C_5 60.1; C_{arom} 122.4-137.3; C_3 149.16; C_{7a} 163.31; C_6 188.15; 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 recristallisation 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 : νC=O : 1719 cm^{-1} ,νC=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 $C_{11}H_8N_4O_2$: %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 : νC=O : 1714 cm^{-1} ,νC=N : 1602 cm^{-1}; ^1H NMR: 1.25(t,$^3J_{HH}$= 7.5, 3H); 2.65(q,$^3J_{HH}$= 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 $C_{12}H_{10}N_4O_2$: %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 : νC=O : 1717 cm^{-1} ,νC=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 $C_{17}H_{12}N_4O_2$: %C 67.10; %H 3.97; %N 18.41. Found %C 67.33; %H 4.15; %N 18.32.

Crystal data for 4a : $C_{11}H_{10}N_4O$, M=214.23; monoclinic crystal system , space group $P2_1/c$, a=7.2001(2), b=10.9071(3), c=13.2681(4) Å, β=103.0320(10)°, V=1015.14(5) $Å^3$, Z=4 , d_{calc}=1.402, T=293(2), R_1 = 0.0461, wR_2 = 0.1206 for 2293 independant reflexions with I >2σ(I) and GOOF=0.963.

Aknowledgement

The X-ray analysis has been realized in « Laboratoire de Cristallographie et Modélisation des Matériaux Minéraux et Biologiques » UMR-CNRS , thus we are grateful to professor Slimane Dahaoui for the facilities provided.

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Received on September 9, 2003.