Regioselective Synthesis of a New [1,2,3]-triazoles Directly from Imidates

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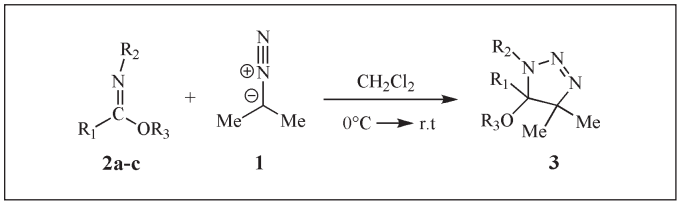

A one pot synthetic approach to the novel [1,2,3]-triazoles system, by 1,3-dipolar cycloaddition of 2-diazopropane to the imidates **2**, is described. The structures of the obtained adducts have been assigned by means of spectroscopic measurements.

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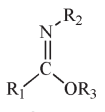
1. Introduction.

[1,2,3]-Triazoles have found wide use in pharmaceuticals agrochemicals, dyes, photographic materials and corrosion inhibition *etc*. [1]. For exemple, there are numerous examples in the literature including anti-HIV activity [2], antimicrobial activity against Gram-positive bacteria [3] and selective adrenergic receptor agonism by means of triazole compounds [4]. Several methods have been described for the synthesis of [1,2,3]-triazoles. Among them, the most important and useful one is the cycloaddition of azides with alkynes [5]. However, this reaction usually needs elevated temperatures and also forms a mixture of 1,4 and 1,5 regioisomers when unsymmetrical alkynes are employed. Recently, studies on 1,4 versus 1,5 regioselectivity were reported. Sharpless used Cu (I) salt as a catalyst to promote the reaction of azide with terminal alkynes in order to generate 1,4–substituted products with high regioselectivity [6]. Meldal [7] also regioselectivity synthesized 1,4–substituted [1,2,3]-triazoles by 1,3-dipolar reactions of azides with polymer-supported terminal alkynes. The initial regioselective 1,3 dipolar addition of diazopropane to imidates **2** constitutes a novel route for the synthesis of [1,2,3]-triazoles. We now report the synthesis of new [1,2,3]-triazoles by regioselective 1,3-dipolar cycloaddition of the versatile 2-diazopropane **1** to imidates **2**.To the best of our knowledge, this reaction has never been reported before.



2a-c

	2a	**2b**	**2c**
R_1	Ph	Ph	Ph
R_2	H	$COmNH_2C_6H_4$	$CO(CH_2)_2$-CH_3
R_3	Me	Me	Me

Figure 1

2. Results and Discussion.

2.1 Preparation and Properties of Imidates **2**.

Imidates **2** were prepared in two steps by first reacting nitrile derivatives with various alcohols. The condensation of the obtained iminoester with appropriate acetyl chloride resulted in the formation of the title compounds **2a-c** (Figure 2).

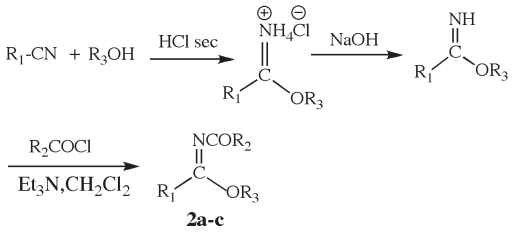


Figure 2

The characterizations of compounds **2a-c** are given in the experimental section. The structures of the products were elucidated by means of spectroscopic analysis.2.2 Cycloaddition Reaction of 2-Diazopropane with Imidates **2a-c**. Synthesis of [1,2,3]-triazoles.

The 2-diazopropane **1** reacts at 0 °C in dichloromethane with the imidate **2a** to give exclusively the adduct **3a** after 10 h of reaction. This compound results from the regioselective 1,3-dipolar cycloaddition of the 2-diazopropane to the imidate C=N bond (Figure 3).

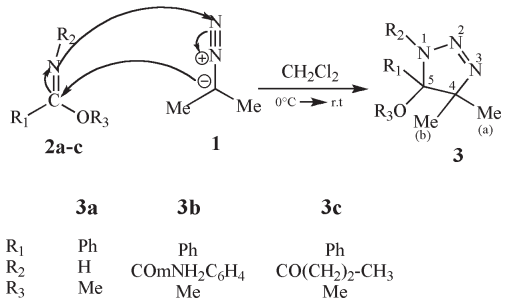


Figure 3

The structure of compound **3a** was determined by ^1H and ^{13} C NMR spectroscopy as well as 2D NMR experiments. The ^1H NMR spectrum shows two singlets at 1.92 ppm and at 1.97 ppm for the methyl protons and at 3.81 ppm for the methoxylic protons. ^{13}C NMR showed a signal at 50.2 ppm corresponding to the methoxy groups and the aromatic carbon resonances appeared between 126.4 ppm and 143.2 ppm.

The methyl protons correlate with C_5 and with the carbon C_4 consistent with the neighbourghing C_4-C_5 connection. The NOESY spectrum shows a nOe correlation between the methoxylic protons and the methyl protons.

Under similar conditions, reaction of imidate **2b** with 2-diazopropane performed at 0 ºC in dichloromethane, was completed in less than 10 hours and gave mainly product **3b**. As before, the structure of **3b** was determined *via* a detailed mono and bidimensional NMR study.

We also investigated the reaction of imidate **2c** with 2-diazopropane to get the corresponding regioisomer **3c**. Data from the elemental analysis indicated that the calculated and observed values are within the acceptable limits (± 0.4%) and have been found to be in conformity with assigned structure. Furthermore the ^{13}C NMR spectrum in $CDCl_3$ is also in agreement with this structure and shows the absence of signal corresponding to the iminic carbone of the starting imidate **2c** at 160 ppm [8].

These results show for the first time, the reactivity of the double bond C=N with the 2-diazopropane that constitutes an efficient route for the preparation of new heterocyclic systems. In all cases, the reaction is periselective: - only the double bond C=N is affected - and regiospecific - diazo carbon attacks the quaternary carbon of the imidate **2** and not the double bond C=O (substrates **2b** and **2c**). Indeed diazopropane reacts with ketones with inverse regioselectivity (with regards to imidates **2**) to yield oxadiazolines [9,10] (Figure 4).

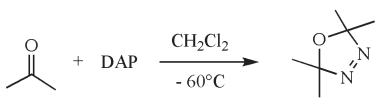


Figure 4

In conclusion, we have been successful in developing a new method for the synthesis of [1,2,3]-triazoles by regioselective 1,3-dipolar cycloaddition of 2- diazopropane with imidates **2** in good yields. Further studies on this reaction and its application in organic synthesis are in progress.

EXPERIMENTAL

General Remarks.

NMR spectra were recorded at room temperature on a BRUKER AC 300 MHz (^1H and ^{13}C), with TMS as an internal standard. Signal assignments were based on HMBC and NOESY experiments. The IR spectra were recorded on a Bruker FT-IR IFS 28 in the region between 4000 and 400 cm^{-1}, (KBr). Elemental analyses were performed at the National Institute of Research and Physicochemical Analysis in Tunisia. Melting points were determined on a Buchi apparatus and are uncorrected. TLC was performed on aluminium backed plates coated with silica gel 60 with F254 indicator. Column chromatography was carried out using silica gel 60. 2-Diazopropane **1** was prepared according to the Staudinger method [11] and conserved in ethereal solution at –78 °C. The mode of filling of the column chromatography and the procedure are described by D. F. Taber [12] and W. C. Still [13].

General Procedure for the Preparation of Imidate **2a-c**.

To a 250 ml round bottom flask, simple imidate (0.1 mole), Et_3N (0.11 mole) and 150 ml of anhydrous ether were added 0.11 mole of the correspond acetyl chloride. The mixture was stirred at r.t for 12 h. The resulting solid was collected by filtration and recrystallized from cyclohexane.

Methyl benzene carboximidoate **(2a)**.

This compound was obtained as white oil in 75 % yield; IR νcm^{-1} (KBr): 1658 (C=N); 3384 (NH). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.75 (s, 3H, O-CH_3); 5.50 (s, 1H, NH); 7.17-7.74 (m,5H,$H_{arom.}$). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 55.3 (O-*C*H_3); 126.45-129.2(C_{arom}); 161.6 (*C*=N).

Anal. Calcd. for C_8H_9NO: C, 71.11; H, 6.66; N, 10.37; O, 11.86. Found. C, 71.1; H, 6.6; N, 10.4; O, 11.9.

3-Amino-*N*-(methoxyphenylmethylene)benzamide (**2b**).

This compound was obtained as a yellow crystalline solid in 70 % yield, mp 122 °C, IR νcm^{-1}, KBr): 1672 (C=N), 1690 (CO); ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, O-CH_3); 6.30-7.32 ,9H, $H_{arom.}$), 8.40 (s, 2H, NH_2); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 53.9 (O-*C*H_3); 124.5-138.5(C_{arom});160.5 (*C*=N); 168.1 (*C*O).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.86; H, 5.51; N, 11.02; O, 12.60. Found: C, 70.80; H, 5.5; N, 10.80; O, 12.9.

Methyl-*N*-butyryl Benzene Carboximidoate **(2c)**.

This compound was obtained as a yellow crystalline solid in 70 % yield, m.p 120°C, IR νcm^{-1} (KBr): 1655 (C=N); 1690 (CO). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.15 (t,3H); 2.33 (q, 2H) ; 3.80 (s,3H); 7.45 (m,5H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 13.1 (*C*H_3); 18.7 (*C*H_2-CH_3); 40.9 (*C*H_2-CO); 54.6 (O-*C*H_3); 126.5-129.7(C_{arom}); 160.6 (*C*=N); 173.9 (*C*O).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.31; N, 6.82; O, 15.62; Found: C, 70.2; H, 7.2; N, 6.9; O, 15.7.

Cycloaddition Reaction of 2-Diazopropane with Imidates **2a-c**: Synthesis of [1,2,3]-Triazoles **3a-c**.

To a stirred solution containing (2 mmoles) of imidate **2a-c** in 40 ml of anhydrous dichloromethane at 0 °C were added, in small fractions, 10 ml of a 2.6 *M* etheral solution of 2-diazopropane freshly prepared at –60 °C. The reaction was followed by TLC (hexane- ethyl acetate 1/1 as eluent) and the reaction was maintained till the imidate **2a-c** had totally reacted. The solution was allowed to react for 10 hours at 0 °C at which time the solvent was evaporated under reduced pressure. The obtained [1,2,3]-triazoles were purified either by filtration on a column of silica or by recristallisation in a mixture of dichloromethane-petroleum ether to afford **3a-b**.

5-Methoxy-4,4-dimethyl-5-phenyl-4,5-dihydro-1*H*-[1,2,3]-triazole **(3a)**.

This compound was obtained as a yellow oil in 70 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.92 (s, 3H, $CH_{3(a)}$); 1.97 (s, 3H, $CH_{3(b)}$); 3.74 (s, 3H, O-CH_3); 5.60 (s, 1H, NH); 7.17-7.74 (H_{arom}.); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 17.9 (*C*$H_{3(a)}$); 19.23 (*C*$H_{3(b)}$); 50.2 (O-*C*H_3); 82.7 (C_4); 103.75 (C_5); 126.45-143.2(C_{arom}). IR νcm^{-1} (KBr): 1525 (N=N); 3020 (C-C_{arom}); 3200 (NH); 3020 (C-C_{arom}).

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.39; H, 7.31; N, 20.48; O, 7.80. Found: C, 64.3; H, 7.2; N, 20.4; 0, 7.6.

3-[(5-Methoxy-4,4-dimethyl-5-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)carbonyl]aniline **(3b)**.

This compound was obtained as a yellow oil in 75 % yield, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.21 (s, 3H, $CH_{3(a)}$); 1.22 (s, 3H, $CH_{3(b)}$); 3.90 (s, 3H, O-CH_3); 6.30-7.32 (H_{arom}.); 8.40 (s, 2H, NH_2); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 17.3 (*C*$H_{3(a)}$); 19.3 (*C*$H_{3(b)}$); 57.3(O-*C*H_3); 81.4 (C_4); 102.3 (C_5); 124.2-140.5(C_{arom}); IR νcm^{-1} (KBr): 1620 (N=N); 3030 (C-C_{arom}).

Anal. Calcd. for $C_{12}H_{15}N_4O_2$: C, 58.06 ; H, 6.45; N, 22.58; O, 12.91.Found : C, 57.8; H, 6.4; N, 22.5; 0, 13.3.

5-Methoxy-4,4-dimethyl-5-phenyl-1-propionyl-4,5-dihydro-1*H*-[1,2,3]-triazole **(3c)**.

This compound was obtained as a yellow crystal in 80 % yield; m.p = 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.26 (s, 3H, $CH_{3(a)}$); 1.20 (t, 3H); 1.28 (s, 3H, $CH_{3(b)}$) ; 2.30 (q, 2H); 3.85 (s, 3H, O-CH_3); 6.30-7.32 (H_{arom}); 7.55 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 16.9 (*C*$H_{3(a)}$); 19.5(*C*$H_{3(b)}$); 21.9(*C*H_3); 22.3 (*C*H_2-CH_3); 33.3 (*C*H_2-CO); 55.2 (O-*C*H_3); 83.4 (C_4); 102.5 (C_5); 124.2-142.5(C_{arom}). IR νcm^{-1} (KBr): 1625 (N=N); 3020 (C-C_{arom}).

Anal. Calcd. for $C_9H_{17}N_3O_2$: C, 54.27 ; H, 8.54; N, 21.10; O, 16.08. Found: C, 54.2; H, 8.5; N, 21.2; 0, 16.1.

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