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Regioselective synthesis of a new [1, 2, 3] - triazoles directly from imidates

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ABSTRACT

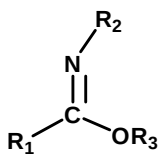
A one pot synthetic approach to the novel [1, 2, 3] triazoles system, by 1, 3- dipolar cycloaddition of phenyldiazomethane to the imidates **(2)**, is described. The structures of the obtained adducts have been assigned by means of spectroscopic measurements.

KEYWORDS

Periselectivity;
Cycloaddition;
Regioselctivity;
Triazole.

INTRODUCTION

[1,2,3]-triazoles have found wide use in pharmaceuticals agrochemicals, dyes, photographic materials and corrosion inhibition etc.[1]. For expemple, there are numerous examples in the literature including anti- HIV activity[2], antimicrobial activity against Gram positive bacteria[3]. 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 azide with alkyne[5]. However, this reaction usually needs elevated temperature and also forms a mixture of 1,4 and 1,5 regioismers for unsymmetrical alkynes. Recently, studies on 1,4 versus 1,5 regioselectivity were reported. Sharpless[6]. Used Cu (I) salt as a catalyst to promote the reaction of azide with terminal alkynes to give in high regioselectivity 1,4 – substituted products. Meldal[7] also regioselectivity synthesized 1,4 – substituted [1, 2, 3]- triazoles by 1,3- dipolar reaction of azides with polymer- supported terminal alkynes. The initial regioselective 1,3 dipolar addition of phenyldiazomethane 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 phenyldiazomethane to imidates **(2)**. The litterature does not bring back any study concerning the reactivity of such compounds with the phenyldiazomethane. (Scheme 1).



(2a-c)

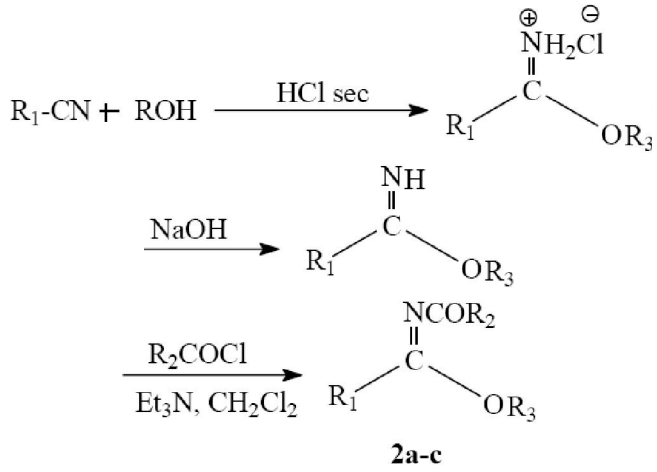
	2a	2b	2c
R_1	Ph	Ph	Ph
R_2	H	$COmNH_2C_6H_4$	$CO(CH_2)_2CH_3$
R_3	Me	Me	Me

Scheme 1

RESULTS AND DISCUSSION

Preparation and properties imidates 2

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



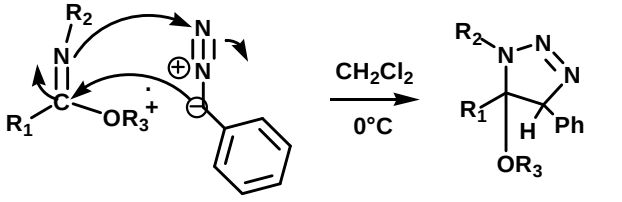
2a-c

Scheme 2

Some characterizations of **(2a-c)** were given in the experimental section. The structure of the obtained compounds was elucidated by spectral data and was given in the experimental section.

Cycloaddition reaction of phenyldiazomethane with imidates 2a-c. Synthesis of [1, 2, 3]- triazoles

The phenyldiazomethane **(1)**, reacts at 0°C with imidate **(2a)** in dichloromethane and exclusively gives, after 10 h of reaction, only the adduct **(3a)** isolated in 70 % yield and corresponding to the regioselective 1,3-dipolar cycloaddition of the phenyldiazomethane to the imidate C=N bond (Scheme 3).



	3a	3b	3c
R_1	Ph	Ph	Ph
R_2	H	$COmNH_2C_6H_4$	$CO(CH_2)_2CH_3$
R_3	Me	Me	Me

Scheme 3 : Cycloaddition reaction of phenyldiazomethane with imidates (2a-c)

The structure of this compound **(3a)** was determined by ^1H and ^{13}C NMR spectroscopy. 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. In ^{13}C a signal at 50.2 ppm corresponds to the methoxy groups. The aromatic carbons appeared between 126.4 ppm and 143.2 ppm.

The addition regioselectivity in **(3a)** formation was established by ^1H-^{13}C HMBC 2D- NMR that shows the C_5-C_4-Me linkages.

The H_4 proton correlate with C_5 and with the carbon C_4 consistent with the neighbourghing C_4-C_5 connexion. The NOESY spectrum shows a nOe cross between the methoxylic protons and the H_4

Under similar conditions, reaction of imidate **(2b)** with phenyldiazomethane performed at 0°C in dichloromethane, was completed in less than 10 hours and gave mainly product **(3b)** of simple substitution. The structure of **(3b)** was determined via a detailed mono and bidimensional NMR study.

We also investigated reaction of imidate **(2c)** with phenyldiazomethane to get the corresponding regioisomer **(3c)**. Data from the elemental analysis indicated that the calculated and observed values were 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 at 160 ppm[8], of the starting imidate **(2c)** what implies its engagement in this reaction of cycloaddition with the phenyldiazomethane

These results involves for the first time, the reactivity of the double bond C=N with the phenyldiazomethane; that constitutes an efficient route for the preparation of new heterocyclic systems. In all the 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.

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 phenyldiazomethane with imidates to good yield. Further studies on this reaction and its application in organic synthesis are in progress.

Full Paper

EXPERIMENTAL SECTION

General remarks

NMR spectra were recorded at room temperature on a AC 300 MHz in $CDCl_3$. Chemical shifts are expressed in ppm downfield from $SiMe_4$ (^1H and ^{13}C). 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 this institute. Melting points were determined on a Buchi apparatus and were uncorrected. TLC was performed on aluminum – backed plates coated with silica gel 60 with F254 indicator. Column chromatography was carried out on a silica gel 60. The mode of filling of the column and the procedure are those described by D.F.TABER[11] and W.C.STILL[12].

General procedure for the preparation of imidate (2a-c)

To a 250 ml round bottle, 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 12h. The resulting solid was filtered and recrystallized from cyclohexane

Imidate (2b) (Yellow crystal)

Yield: 70 %; M.P 122ªC, IR νcm^{-1} (KBr): 1690 (CO), 1672 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ : 3.82 (s,3H, O-CH_3); 8.40 (s, 2H, NH_2) ; 6,30-7,32 (H_{arom}.)

Imidate (2c) (White needles)

Yield: 80 %; M.P 120ªC, IR νcm^{-1} (KBr): 1690 (CO), 1655 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ : 1.15 (t,3H); 2.33 (q, 2H) ; 3.80 (s,3H), 7.45 (m,5H).

Imidate (2a) (White oil)

Yield: 75 %; IR νcm^{-1} (KBr): 3384 (NH), 1658 (C=N). ^1H NMR (300 MHz, $CDCl_3$) δ : 3.75 (s,3H, O-CH_3); 5.50 (s, 1H, NH) ; 7.17-7.74 (H_{arom}.).

Cycloaddition reaction of phenyldiazomethane with imidates (2a-c). Synthesis [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 phenyldiazomethane freshly prepared at –60 °C. The reaction was followed by TLC (hexane- ethylacetate 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 and the solvent was evaporated under reduced pressure. The obtained [1,2,3]-triazoles was purified according to the case by filtration on a column of silica or by recristallisation in a mixture of dichloromethane- petroleum ether to afford **(3a-b)** with the following characteristics:

5- methoxy- 4-phenyl -5- phenyl- 4,5- dihydro-1H-[1,2, 3] triazole: 3a (Yellow oil)

Yield: 70 %; ^1H NMR (300 MHz, $CDCl_3$) δ: 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 ($CH_{3(a)}$); 19.23 ($CH_{3(b)}$); 50.2 (O-CH_3); 82.7 (C_4); 103.75 (C_5), 126.45-143.2(C_{arom}). IR νcm^{-1} (KBr): 3200 (NH), 3020 (C-C_{arom}), 1525 (N=N). $C_{11}H_{15}N_3O$ Calcd. 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.

5- methoxy- 4-phenyl -5- phenyl- 4,5- dihydro-1-(3-amino-phenyl) ethanone [1,2, 3] triazole: 3b (Yellow oil)

Yield: 75 %; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s,3H, O-CH_3); 8.40 (s, 2H, NH_2); 6.30-7.32 (H_{arom}.). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 17.3 ($CH_{3(a)}$); 19.3 ($CH_{3(b)}$); 57.3(O-CH_3); 81.4 (C_4); 102.3 (C_5), 124.2-140.5(C_{arom}). IR νcm^{-1} (KBr): 3030 (C-C_{arom}), 1620 (N=N). $C_{12}H_{15}N_4O_2$ Calcd. 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-phenyl -5- phenyl- 4,5- dihydro-1-(pentan-2-one) [1,2, 3] triazole: 3c (Yellow cristal)

Yield: 80 %; MP = 130°C, ^1H NMR (300 MHz, $CDCl_3$) δ: 1.20 (t, 3H); 2.30 (q, 2H); 3.85 (s, 3H), 7.55 (m,5H). 3.85 (s,3H, O-CH_3); 6.30-7.32 (H_{arom}). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 21.9(CH_3); 22.3 (CH_2); 33.3 (CH_2), 16.9 ($CH_{3(a)}$); 19.5($CH_{3(b)}$); 55.2 (O-CH_3); 83.4 (C_4); 102.5 (C_5), 124.2-142.5(C_{arom}). IR νcm^{-1} (KBr): 3020 (C-C_{arom}), 1625 (N=N). $C_9H_{17}N_3O_2$ Calcd. 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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