Condensation of iminoethers with diarylnitrilimines Novel synthesis of 1,2,4-triazoles

A. Romdhane, R. Gharbi, Z. Mighri *

Laboratoire de Chimie des Substances Naturelles et de Synthèse Organique, Département de Chimie, Faculté des Sciences de Monastir, 5019 Monastir, Tunisie

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ABSTRACT : Condensation of iminoethers **3a-c** with diarylnitrilimines **2a-d** led to the corresponding 1,2,4-triazoles **5a-i** in good yields. A probable mechanism was proposed for the reaction and the structure of all obtained products was determined on the basis of their analytical data; ^{1}H, ^{13}C NMR and mass spectrometry.

Key words : Iminoethers, Diarylnitrilimines, 1,2,4-Triazoles.

RESUME : Dans ce travail, nous montrons que la condensation d'iminoéthers **3a-c** avec les diarylnitrilimines **2a-d** permet d'accéder aux 1,2,4-triazoles **5a-i** avec de bons rendements. Les structures des composés obtenus ont été déterminées à l'aide de techniques spectroscopiques telles que la RMN du ^{1}H, du ^{13}C et la spectrométrie de masse.

Mots clés : Iminoéthers, Diarylnitrilimines, 1,2,4-Triazoles.

INTRODUCTION

The 1,2,4-triazole derivatives represent an important class of biologically active compounds. Since the 1,2,4-triazole nucleus is associated with diverse pharmacological activities such as antibacterial [1], antifungal [2], hypoglycaemic [3], antihypertensive [4] and analgesic [5] properties, several methods for the preparation of 1,3,5-trisubstituted-1,2,4-triazoles have been reported [6-9]. Particularly, 1,3-dipolar cycloaddition reaction represents an useful synthetic method for the preparation of such five membered-ring heterocycles. Huisgen *et al.* [10] first described the synthesis of a variety of triazoles from diarylnitrilimines and aldoximes, azines and acetimidic acid esters. In a more recent work, the preparation of fully-aromatised 1,2,4-triazoles through reaction between diarylnitrilimines with azetines was reported [11].

In continuation of our research directed towards the study on the reactivity of iminoethers and their use as versatile synthons in organic synthesis [12], we report here, a novel one-step synthesis of 1,3,5-trisubstituted-1,2,4-triazoles **5a-i** by condensation of iminoethers **3a-c** with a series of diarylnitrilimines **2a-d**.

RESULTS AND DISCUSSION

Treatment of N'-phenylbenzohydrazonoyl chloride **1a-d** with triethylamine released the corresponding diarylnitrilimines **2a-d** which were reacted *in situ* with iminoethers **3a-c** and gave rise to 1,3,5-trisubstituted-1,2,4-triazoles **5a-i** *via* tbe non-isolable intermediates **4**. In order to find out the best conditions for the synthesis of compounds **5**, we examined the reaction under various experimental conditions by changing the temperature and the solvent. Thus, we bave found that the best yields were reached on heating the starting materials in toluene in the presence of an equivalent amount of triethylamine. Taking into account previous studies [7,15] concerning the regiospecificity of 1,3-dipolar cycloaddition of diarylnitrilimines on the C=N bond, we have anticipated that 1,2,4-triazoles would he regiospecifically formed. The reaction progress monitored

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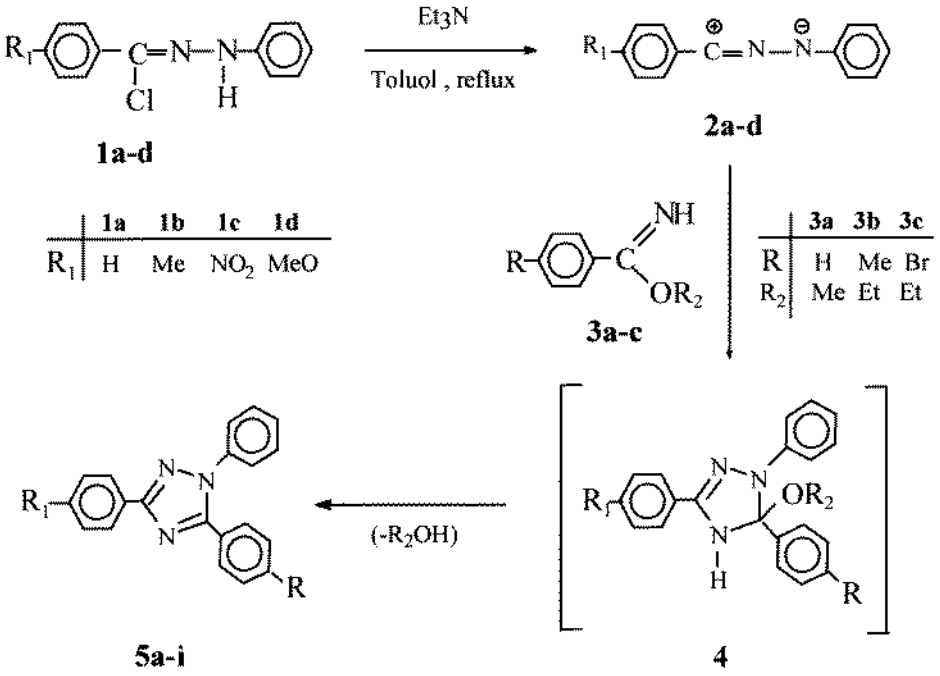
by thin layer chromatography (eluent petroleum ether - ethyl acetate, 9:1) revealed the expected formation of a single cycloadduct wich was, on the basis of its spectral data, assigned as 1,3,5-trisubstituted-1,2,4-triazoles **5.**



	5a	5b	5c	5d	5e	5f	5g	5h	5i
R	Me	Br	H	Me	Br	H	Me	Me	Br
R_1	H	H	Me	Me	Me	NO_2	NO_2	MeO	MeO

Scheme 1 . Synthetic pathway for compounds **5**.

All the examined compounds showed correct protonated molecular peak (MH^+). Furthermore NMR spectra provide evidence to the suggested cycloaddition, thus ^1H NMR spectra exhibited set of signals relative to aromatic and alkyl groups protons for which chemical shifts and multiplicitys were in good agreement with the proposed structure (see experimental section). Unambiguous proofs for the ohtained cycloadducts regiochemistry arised from their ^{13}C data (Table 1). Particularly the high shift-values attributed to the quaternary carbons C-3 and C-5 (160.0-162.4 ppm and 153.6-161.1 ppm, respectively) agree with the strong deshielding effect caused by nitrogens proximity; according to anteriorly described 1,2,4-triazoles [6,7,15]. On an other hand previously published spectroscopic data, showed that 1,2,3-triazoles ring-carbons chemical shift would not exceed 130-140 ppm [16].

From a mechanistic point of view, the reaction process is assumed to follow a two-steps pathway. Primly, iminoethers **3** should react with diarylnitrilimines **2** through 1,3-dipolar cycloaddition reaction. The non-isolable intermediates **4** then undergo, further heteroaromatization by loss of alcohol molecule to afford final isolable 1,2,4-triazoles **5**.

Tahle 1. ^{13}C chemical shifts for compounds **5a-i.**

Comp. / δ (ppm)	C_3	C_5	R = $\underline{C}H_3$	R_1 = $\underline{C}H_3$	R_3 = O$\underline{C}H_3$	$C_{arom.}$
5a	161.9	154.9	21.4	-	-	125.2 - 140.2
5b	162.4	154.1	-	-	-	124.9 - 138.5
5c	162.4	155	-	21.8	-	125.8 - 139.7
5d	162.3	155.1	21.7	21.8	-	125.6 - 140.4
5e	162.2	153.6	-	21.4	-	124.5 - 139.5
5f	160	155.4	-	-	-	123.9 - 148.3
5g	160.3	155.9	21.8	-	-	124.3 - 148.7
5h	162.1	161	21.7	-	55.6	114.3 - 155.1
5i	162.3	161.1	-	-	55.6	114.3 - 153.9

CONCLUSION

Since the cycloaddition reaction of diarylnitrilimines with a variety of compounds containing the C=N double bond [7,15], have found wide-spread uses for the synthesis of various five-membered hctcrocycles incorporating the -C=N-N- unit, thc one-step synthesis we described above illustrates a simple and efficient new method for the preparation of 1,3,5-trisubstituted-1,2,4-triazoles **5** in good yield *via* reaction between diarylnitrilimines **2** and iminoethers **3**.

MATERIALS AND METHODS

General experimental procedures:

Melting points were meseard using cappilary Büchi 510 apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C using TMS as internal standard and $CDCl_3$ as solvent. Coupling constants are given in Hz. Mass spectra were recorded on a MR-SX102 spectrometer using FAB^+ technical. Starting materials wcrc prepared using standard methods [13-14].

Preparation of 2,3,5-trisubstituted-1,2,4-triazoles 5:

In a typical procedure, to a stirred solution of N'-phenylbenzohydrazonoyl chloride 1 (1mmol) and iminoether 3 (1.2 mmol) in dry Toluene (30 mL), was added dropwise over 10 min a solution of triethylamine (1.2 m.mol) in 5 mL of Toluol *via* syringe. The mixture was refluxed for 3 hours under nitrogen. Thc reaction evolution was cheked by TLC. When all the starting materials was consumed, the mixture was cooled to room temperature, then the solvent was evaporated off and the crude was purified by chromatography on a silica gel column using : petroleum ether-ethyl acetatc (9:1).

5a : **5-(4-mehtyl)phenyl-1,3-diphenyl-[1,2,4]triazole**; Yield (%): 75; mp: 99 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.3 (s, 3H), 7.1 (d, J = 8.1 Hz, 2 $H_{arom.}$), 7.2-7.4 (m, 10 $H_{arom.}$), 8.2 (d, J = 8.1 Hz, 2 $H_{arom.}$); FABMS m/z (rel. Int.) 312 (MH^+) (100 %), 207 (5 %), 194 (12 %), 135 (10 %), 91 (11 %), 73 (15 %), 55 (7 %), 43 (5 %).

5h : **5-(4-bromo)phenyl-1,3-diphenyl-[1,2,4]triazole**; Yield (%): 76; mp: 123 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4-7.6 (m, 10 $H_{arom.}$), 7.6 (d, J = 8.7 Hz, 2 $H_{arom.}$), 8.3 (d, J = 8.7 Hz, 2 $H_{arom.}$);

FABMS m/z (rel. Int.) 377 (MH^+) (65 %), 209 (20 %), 197 (55 %), 135 (100 %), 91 (10 %), 73 (27 %), 55 (7 %).

5c : **3-(4-mehtyl)phenyl-1,5-diphenyl-[1,2,4]triazole**; Yield (%): 80; mp : 143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H), 7.2 (d, J = 8.1 Hz, 2 $H_{arom.}$), 7.5 (m, 10 $H_{arom.}$), 8.1 (d, J = 8.1 Hz, 2 $H_{arom.}$); FABMS m/z (rel. Int.) 312 (MH^+) (100 %), 311 (22 %), 197 (13 %), 135 (30 %), 73 (50 %), 55 (50 %), 43 (37 %).

5d : **3,5-his(4-mehtyl)phenyl-1-phenyl-[1,2,4]triazole**; Yield (%): 78; mp: 122 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.3 (s, 3H), 2.4 (s, 3H), 7.1 (d, J = 8.1 Hz, 2 $H_{arom.}$), 7.3 (m, 9 $H_{arom.}$), 8.1 (d, J = 8.1 Hz, 2 $H_{arom.}$); FABMS m/z (rel. Int.) 326 (MH^+) (10 %), 281 (7 %), 207 (21 %), 191 (19 %), 147 (33 %), 133 (18 %), 73 (100 %), 43 (24 %), 28 (18 %).

5e : 5-(4-hromo)phenyl-3-(4-methyl)phenyl-1-phenyl-[1,2,4]triazole; Yield (%): 82; mp:135 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H), 7.2 (d, J = 8.1 Hz, 2 $H_{arom.}$), 7.4 - 7.6 (m, 9 $H_{arom.}$), 8.1 (d, J = 8.1 Hz, 2 $H_{arom.}$); FABMS m/z (rel. Int.) 391 (MH^+) (9 %), 327 (13 %), 281 (10 %), 207 (21 %), 193 (22 %), 136 (42 %), 91 (45 %), 73 (100 %), 41 (26 %).

5f : **3-(4-nitro)phenyl-1,5-diphenyl-[1,2,4]triazole**; Yield (%): 83; mp: 184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3-7.5 (m, 8 $H_{arom.}$), 7.6 (d, J = 7.8 Hz, 2 $H_{arom.}$), 8.3 (d, J = 7.8 Hz, 2 $H_{arom.}$), 8.4 (d, 2 $H_{arom.}$); FABMS m/z (rel. Int.) 343 (MH^+) (17 %), 327 (10 %), 281 (15 %), 221 (12 %), 197 (23 %), 135 (64 %), 73 (100 %), 55 (46 %), 43 (27 %).

5g : **5-(4-mehtyl)phenyl-3-(4-nitro)phenyl-1-phenyl-[1,2,4]triazole**; Yield (%): 87; mp: 127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H), 7.3 (m, 9 $H_{arom.}$), 8.3 (d, J = 7.8 Hz, 2 $H_{arom.}$), 8.5 (d, J = 7.8 Hz, 2 $H_{arom.}$); FABMS m/z (rel. Int.) 357 (MH^+) (42 %), 311 (10 %), 281 (11 %), 207 (16 %), 147 (37 %), 136 (30 %), 91 (25 %), 73 (100 %), 55 (21 %), 43 (13 %).

5h : **3-(4-methoxy)phenyl-5-(4-methyl)phenyl-1-phenyl-[1,2,4]triazole**; Yield (%): 73; mp: 146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H), 4.0 (s, 3H), 7.1 (d, J = 9 Hz, 2 $H_{arom.}$), 7.2 (d, J = 7.8 Hz, 2 $H_{arom.}$), 7.5 (m, 5 $H_{arom.}$), 7.6 (d, J = 7.8 Hz, 2 $H_{arom.}$), 8.2 (d, J = 9 Hz, 2 $H_{arom.}$); FABMS m/z (rel. Int.) 342 (MH^+) (100 %), 213 (2 %), 123 (7 %).

5i : **5-(4-hromo)phenyl-3-(4-methoxy)phenyl-1-phenyl-[1,2,4]triazole**; Yield (%): 77; mp: 195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.7 (s, 3H), 6.9 (d, J = 9 Hz, 2 $H_{arom.}$), 7.3-7.6 (m, 7 $H_{arom.}$), 7.42 (d, J = 8.7 Hz, 2 $H_{arom.}$), 8.0 (d, J = 8.7 Hz, 2 $H_{arom.}$); FABMS m/z (rel. Int.) 406 (MH^+) (28 %), 327 (10 %), 197 (36 %), 135 (100 %), 91 (62 %), 55 (95 %), 43 (73 %).

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