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Reaction of Nitrilimines with Keto-Alkoxycarbonyl-Hydrazones: Synthesis of Substituted 1,2,4-Triazoles and Heterocyclic Spiro Compounds

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Hydrazonoyl halides **(1)** react with alkanone and cycloalkanone alkoxycarbonylhydrazones **(3)** to give the cycloaddition products 4,5-dihydro-1,2,4-triazoles **(7a–h)** rather than the tetrazine cyclo-condensation products. Reaction of **(7c, d)** with hydoxylamine gave the corresponding oximes **(8c, d)** of these heterocycles.

Key Words: Reaction, Nitrilimines, Keto-alkoxycarbonyl hydrazones, Spiro compounds.

INTRODUCTION

Nitrilimines are reported to react with hydrazones in different ways. The reaction with methylhydrazones of aliphatic aldehydes and ketones provides the tetrahydrotetrazines **(6)**[1]. On the other hand, methylhydrazones of aromatic aldehydes give a mixture of cyclic and acyclic tetrazines[2–5]. Simple hydrazones of aliphatic aldehydes and ketones react with nitrilimines to give acyclic addition products **(4)**, which upon heating with palladium-carbon cyclize to 1,6-dihydro-S-tetrazines[6]. Substituted 1,2,4-triazoles find many useful applications as biological reagents, dyes and photographic chemicals.[7] The synthesis of polymers derived from triazoles is currently the most important practical application of this heterocyclic system.[8]

EXPERIMENTAL

Melting points were determined on Electrothermal Melting Temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared spectrometer (KBr discs). ^{1}H- and ^{13}C-NMR spectra were recorded on a Brucker 300 MHz instrument for solutions in $CDCl_3$ at 21°C, using TMS as an internal reference. Electron impact mass spectra were run on Finnigan Mat 8200 and 8400

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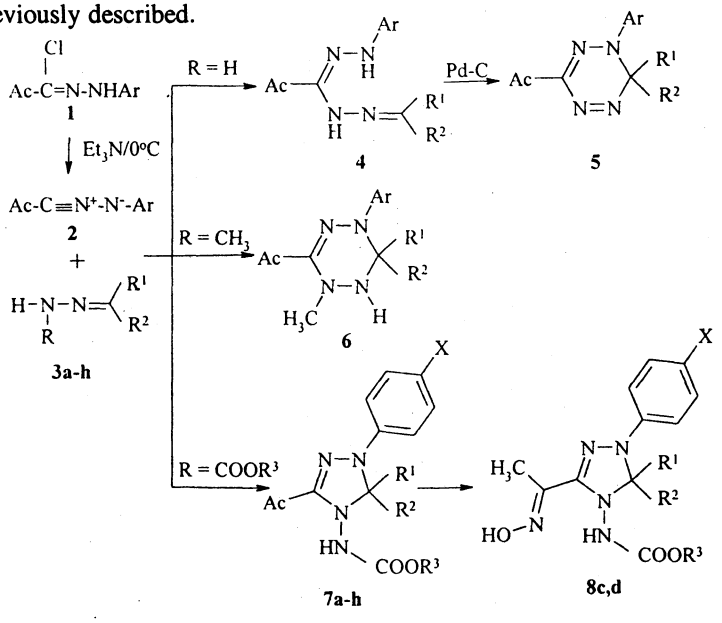
spectrometers at 70 eV. Hydrazonoyl halides[4] (**1**), Hydrazones[6] (**3**) were prepared as previously described.



For R^1, R^2 and Ar of compounds **4**, **5**, and **6** see the original literature

7	a	b	c	d	e	f	g	h
R^1, R^2	Me, Me	Et, Et						
R^3	Me	Me	Et	Et	Et	Et	Et	Et
X	Cl	Cl	Cl	Br	Cl	Cl	Cl	Cl

Scheme-1

Synthesis of Substituted Heterocyclic Spiro Compounds (7)

Triethylamine (5.0 g, 0.05 mol) in absolute tetrahydrofuran (10 mL) was added dropwise to a stirred solution of hydrazonoyl halides (**1**) (0.015 mol) and hydrazones (0.03 mol) in tetrahydrofuran (100 mL) at 0–10°C. The temperature of the reaction mixture was then allowed to rise slowly to room temperature and stirring was continued overnight. The solvent was then evaporated in *vacuo*, and the residual solid was washed with water to remove the triethylamine salt. The crude product was recrystallized from ethanol (20 mL). The yields are those of the pure products as indicated by TLC and their sharp melting points. The following compounds were synthesized using this method:

3-Acetyl-1-(4-chlorophenyl)-4,5-dihydro-4-methoxycarbonylamino-5,5-dimethyl-1H-1,2,4-triazole (7a)

From 2.3 g (0.01 mol) of **1**: 1.56 g (0.015 mol) of **3a**, yield 2.2 g (67%); ^{1}H NMR: 7.3 (m, 4H, aromatic protons), 6.9 (s, 1H, NH), 3.7 (s, 3H, CH_3O), 2.5 (s,

3H, CH_3CO); 1.5 (s, 6H, $2CH_3$ at C5); ^{13}C NMR: 189.65 (C=O), 157.87 (COO), 144.45 (C=N), 141.00, 129.03, 128.07, 119.49 (4 aromatic carbons), 89.11 (C-5 carbon), 53.17 (OCH_3), 29.70 ($2CH_3$ at C5), 26.15 (**CH_3**C=O); IR (cm^{-1}) 3264 ν(NH), 1732 ν(COO), 1684 ν(C=O).

3-Acetyl-1-(4-chlorophenyl)-4,5-dihydro-5,5-diethyl-4-methoxycarbonyl-amino-1H-1,2,4-triazole (7b)

From 2.3 g (0.01 mol) of **1**: 2.37 g (0.015 mol) of **3b**, yield 1.73 g (49%); ^1H NMR: 7.2 (m, 4H, aromatic protons), 6.6 (s, 1H, NH), 3.8 (s, 3H, CH_3O), 2.4 (s, 3H, CH_3CO); 2.0 (m, 2H, CH_2), 1.8 (m, 2H, CH_2), 0.8 (m, 6H, $2CH_3$); ^{13}C NMR: 188.51 (C=O), 158.00 (COO), 143.72 (C=N), 140.91, 129.18, 126.35, 116.20 (4 aromatic carbons), 93.06 (C-5 carbon), 53.18 (OCH_3), 28.00 ($2CH_2$ at C5), 26.26 (**CH_3**C=O), 7.59 (CH_2**CH_3**); IR (cm^{-1}) 3277 ν(NH), 1736 ν(COO), 1676 ν(C=O).

3-Acetyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro [4.4] non-2-ene (7c)

From 2.3 g (0.01 mol) of **1**: 2.55 g (0.015 mol) of **3c**, yield 3.1 g (87%); ^1H NMR: 7.3–7.1 (4H, aromatic protons), 6.8 (s, 1H, NH), 4.2 (q, 2H, OCH_2), 2.5 (s, 3H, CH_3CO), 2.2–1.7 (m, 8H, cyclopentane protons), 1.3 (t, 3H, CH_3); ^{13}C NMR: 189.37 (C=O), 157.42 (COO), 143.81 (C=N), 140.12, 129.00, 127.29, 118.47 (4 aromatic carbons), 97.28 (C-5 ring spiro carbon), 62.39 (OCH_2), 26.04 (**CH_3**C=O), 34, 24.90 (cyclopentane carbons), 14.41 (CH_3); IR (cm^{-1}) 3262 ν(NH), 1717 ν(COO), 1686 ν(C=O).

3-Acetyl-1-(4-bromophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro [4.4] non-2-ene (7d)

2.75 g (0.01 mol) **1**: 2.55 g (0.015 mol) **3d,** yield = 2.6 g (64%); ^1H NMR: 7.4–7.0 (4H, aromatic protons), 6.9 (s, 1H, NH), 4.1 (q, 2H, OCH_2), 2.4 (s, 3H, CH_3CO), 2.2–1.7 (m, 8H, cyclopentane protons), 1.2 (t, 3H, CH_3); ^{13}C NMR: 189.37 (C=O), 157.42 (COO), 143.81 (C=N), 140.52, 131.92, 118.61, 114.64 (4 aromatic carbons), 97.19 (C-5 ring spiro carbon), 62.39 (OCH_2), 26.04 (**CH_3**C=O), 33.0, 24.90, (cyclopentane carbons), 14.46 (CH_3); IR (cm^{-1}) 3262 ν(NH), 1723 ν(COO), 1683 ν(C= O).

3-Acetyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro [4.5] dec-2-ene (7e)

2.3 g (0.01 mol) **1:** 2.8 g (0.015 mol) **3e**, yield = 2.7 g (71%); ^1H NMR: 7.3–7.2 (4H, aromatic protons), 6.9 (s, 1H, NH), 4.1 (q, 2H, OCH_2), 2.4 (s, 3H, CH_3CO), 1.9–1.6 (m, 10H, cyclohexane protons), 1.2 (t, 3H, CH_3); ^{13}C NMR: 189.50 (C=O), 156.96 (COO), 145.47 (C=N), 140.22, 128.9, 122.77, 115.19 (4 aromatic carbons), 88.38 (C-5 ring spiro carbon), 62.00 (OCH_2), 25.99 (**CH_3**C=O), 34, 24.67, 22.51 (cyclohexane carbons), 14.48 (CH_3); IR (cm^{-1}) 3267 ν(NH), 1723 ν(COO), 1683 ν(C=O).

3-Acetyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-8-methyl-1,2,4-triaza-spiro [4.5] dec-2-ene (7f)

2.3 g (0.01 mol) **1:** 3.0 g (0.015 mol) **3f**, yield = 2.3 g (57%); ^{1}H NMR shows signal coupling: 7.3–7.2 (4H, aromatic protons), 6.96, 6.88 (s, 1H, NH), 4.1 (q, 2H, OCH_2), 2.42, 2.40 (s, 3H, CH_3CO), 2.0–1.1 (m, 9H, cyclohexane protons), 1.2 (t, 3H, CH_3), 0.86, 0.84 (s, 3H, CH at cyclohexyl group); ^{13}C NMR shows signal doubling: 189.71, 189.52 (C=O), 157.24, 156.92 (COO), 145.71, 145.44 (C=N), (141.31, 140.09), (129.58, 128.91), (125.00, 122.49), (115.75, 115.15) (4 aromatic carbons), (89.34, 88.05) (C-5 ring spiro carbon), (62.10, 61.10) (OCH_2), (26.12, 26.00) ($\mathbf{CH_3}$C=O), (34.80, 33.62), (29.37, 28.05), (22.05, 19.06) (cyclohexane carbons), (31.29, 31.18) (CH_3 at cyclohexane), (14.48, 14.11) (CH_3); IR (cm^{-1}) 3254 ν(NH), 1720 ν(COO), 1689 ν(C=O).

3-Acetyl-8-tert-butyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro [4.5] dec-2-ene (7g)

2.8 g (0.01 mol) **1:** 3.4 g (0.02 mol) **3g**, yield = 2.3 g (54%); ^{1}H NMR: 7.3–7.2 (m, 4H, aromatic protons), 6.8 (s, 1H, NH), 4.1 (q, 2H, OCH_2), 1.2 (t, 3H, CH_3), 2.5 (s, 3H, CH_3CO), 2.0–0.9 (m, 9H, cyclohexane protons), 0.82 (s, 9H tert-butyl group); ^{13}C NMR: 189.50 (C=O), 156.80 (COO), 145.54 (C=N), 140.12, 128.90, 122.64, 115.23 (aromatic carbons), 88.13 (C-5 ring spiro carbon), 62.01 (OCH_2), 46.67, 41.30, 32.42, 27.50, 23.54 (tert-butylcyclohexane carbons), 25.94 ($\mathbf{CH_3}$C=O), 14.45 (CH_3); IR (cm^{-1}) 3252 ν(NH), 1721 ν(COO), 1687 ν(C=O).

3-Acetyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro [4.6] undec-2-ene (7h)

0.7 g (0.003 mol) **1:** 1.0 g (0.004 mol) 3h, yield = 0.71 g (55%); ^{1}H NMR: 7.3 –7.2 (4H, aromatic protons), 6.8 (s, 1H, NH), 4.1 (q, 2H, OCH_2), 2.4 (s, 3H, CH_3CO), 2.1–1.3 (m, 12H, cycloheptane protons), 1.2 (t, 3H, CH_3); ^{13}C NMR: 189.63 (C=O), 157.30 (COO), 144.77 (C=N), 140.62, 129.16, 122.11, 115.21 (4 aromatic carbons), 93.12 (C-5 ring spiro carbon), 62.27 (OCH_2), 26.03 ($\mathbf{CH_3}$C=O), 43.92, 30.35, 24.37 (cycloheptane carbons), 14.46 (CH_3); IR (cm^{-1}) 3252 ν(NH), 1727 ν(COO), 1684 ν(C=O).

Synthesis of the oximes (8c, d)

To a solution of the respective triazole **1** (3 mmol) in methanol (70 mL) was added hydroxylamine hydrochloride (15 mmol) and sodium acetate (15 mmol). The resulting mixture was stirred overnight at room temperature. The solvent was then evaporated in a dish at room temperature and the residue washed with water (100 mL). The insoluble product was recrystallized from ethanol or chloroform/petroleum ether 40–60°C and left in the refrigerator.

The following compounds were synthesized using this method:

3-Acetyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro [4.4] non-2-ene oxime (8c)

From 1.8 g (0.005 mol) of **7c**: yield 1.17 g (62 %); ^{1}H NMR: 7.2–6.9 (4H, aromatic protons), 9.7 (b.s, 1H, OH), 8.2 (s, 1H, NH), 4.2 (q, 2H, OCH_2), 2.2 (s,

3H, CH_3CO), 2.3–1.5 (m, 8H, cyclopentane protons), 1.2 (t, 3H, CH_3); ^{13}C NMR: (158.93, 157.5) (COO), 147.42 (C=NOH), 144.83 (C=N), 141.32, 128.89, 126.11, 117.89 (4 aromatic carbons), 95.51 (C-5 ring spiro carbon), (62.83, 62.37) (OCH_2), 11.23 ($\mathbf{CH_3}$C=O), (37.27, 30.30), (24.37, 24.03) (cyclopentane carbons), 14.47 (CH_3); IR (cm^{-1}) 3389 ν(OH), 3275 ν(NH), 1717 ν(COO).

3-Acetyl-1-(4-bromophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro [4.4] non-2-ene oxime (8d)

From 2.1 g (0.005 mol) of **7d**: yield 1.2 g (57%); ^1H NMR: 7.3–7.0 (4H, aromatic protons), 10.2 (b.s, ^1H, OH), 8.2 (s, ^1H, NH), 4.2 (q, 2H, OCH_2), 2.2 (s, 3H, CH_3CO), 2.3–1.5 (m, 8H, cyclopentane protons), 1.2 (t, 3H, CH_3); ^{13}C NMR: (158.96, 157.04) (COO), (148.66, 147.52) (C=NOH), (144.80, 144.75) (C=N), (141.80, 141.70), (132.03, 131.77), (118.57, 118.08), (114.61, 113.39) (4 aromatic carbons), (96.15, 95.47) (C-5 ring spiro carbon), (62.86, 62.38) (OCH_2), 11.2 ($\mathbf{CH_3}$C=O), (36.72, 30.73), (24.46, 24.21) (cyclopentane carbons), (14.56, 14.48) (CH_3); IR (cm^{-1}) 3382 ν(O—H), 3274 ν(NH), 1718 ν(COO).

RESULTS AND DISCUSSION

In this work, we found that nitrilimines **(2)** react with alkanone and cycloalkanone alkoxycarbonyl-hydrazones **(3a–h)** to give the substituted triazoles **(7a–h)**.

The assignment of structures **(7)** is based on analytical and spectral data. The electron impact (EI) mass spectra (Table-1) display the correct molecular ions in accordance with the suggested structures. The base peak in all these compounds is that of the conjugated vinyl triazole cation. This occurs at ($M^{+\bullet}$-43, $C_3H_7^{\bullet}$) for compounds containing cyclohexane moiety, ($M^{+\bullet}$-57, $C_4H_9^{\bullet}$) for compounds containing cycloheptane moiety, and ($M^{+\bullet}$-99, $C_7H_{15}^{\bullet}$) for compounds containing tert-butylcyclohexane moiety. This fragmentation pattern is well known in the literature for cycloalkanones.[9]

The ^1H NMR shows a signal at 6.5–7.0 ppm which is characteristic for the N—H of the five-membered ring compounds **(7a–h)**. The N—H of the six-membered ring structure is expected to appear at 4–5 ppm[1]. Signal doubling is observed both in ^1H and ^{13}C NMR spectra of compound **(7f)** containing 4-methylcyclohexane moiety due to tautomeric isomerism. The entire NMR data are presented in the experimental part.

The ^{13}C NMR spectra display the characteristic signals of the suggested structures. The signal for C-5 (quaternary or spiro carbon) appears in the range of 80–90 ppm. This is similar to reported values of quaternary and spiro carbons flanked by two nitrogens in five-membered heterocycles.[10–12] This provides a strong evidence in support of structures **(7a–h)** rather than the six-membered heterocyclic structure **(6)** which is expected to have a C-6 signal at about 70 ppm. The oximes **(8c, d)** of compounds **(7c, d)** were prepared by applying a five fold excess of hydroxylamine hydrochloride in presence of sodium acetate. These oximes are important, since they may be utilized as bidentate ligands.[13]

TABLE -1
PHYSICAL DATA AND MOLECULAR ION PEAKS FOR COMPOUNDS **7a–h** AND **8c, d**

Compd.	m.p. (°C)	Yield (%)	m.f.	$M^{+\bullet}$
7a	163–164	67	$C_{14}H_{17}N_4O_3Cl$	324/326
7b	107–108	49	$C_{16}H_{21}N_4O_3Cl$	352/354
7c	145–146	87	$C_{17}H_{21}N_4O_3Cl$	364/366
7d	149–150	64	$C_{17}H_{21}N_4O_3Br$	408/410
7e	108–109	71	$C_{18}H_{23}N_4O_3Cl$	378/380
7f	117–118	57	$C_{19}H_{25}N_4O_3Cl$	392/394
7g	163–164	54	$C_{22}H_{31}N_4O_3Cl$	434/436
7h	111–112	55	$C_{19}H_{25}N_4O_3Cl$	392/394
8c	152–153	62	$C_{17}H_{22}N_5O_3Cl$	379/381
8d	158–159	57	$C_{17}H_{22}N_5O_3Br$	423/425

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