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Synthesis of Substituted 1,2,4-Triazoles from Reaction of Nitrilimines with Substituted Hydrazones

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Hydrazonoyl halides (1) react with substituted hydrazones of alkanone, cycloalkanone and heterocyclic ketones (**2–4**) to give the cycloaddition products 4,5-dihydro-1,2,4-triazoles (**5–7**). The assignment of structures (**5–7**) was based on spectral data (mass spectra, IR, ^1H and ^{13}C NMR).

Key Words: Nitrilimines, Hydrazones, Triazoles, Cycloaddition reactions, Spiro compounds

INTRODUCTION

1,2,4-Triazoles are by far the best known class of triazoles[1]. They are obtained either by synthesis from acyclic compounds or by transformation of other heterocyclic systems[2].

Different methods employing hydrazines[3] and amidrazones[4] in the synthesis of 1,2,4-triazoles had been reported. Methods employing cycloaddition reactions of nitrilimines with C—N multiple bonds are well known for the synthesis of triazoles and their derivatives. These include cycloaddition to nitriles[5], oximes[6] and hydrazones[7].

Nitrilimines are reported to react differently with hydrazones. The reaction with methylhydrazones of aliphatic aldehydes and ketones provides the tetrahydrotetrazines[8]. On the other hand, methylhydrazones of aromatic aldehydes give a mixture of cyclic and acyclic tetrazines[9]. Simple hydrazones of aliphatic aldehydes and ketones react with nitrilimines to give acyclic addition products, which upon heating with palladium-carbon cyclize to 1,6-dihydro-s-tetrazines[10].

Substituted 1,2,4-triazoles find many useful applications. Some of them are used as analytical reagents for the determination of boron[11], cobalt[12] and antimony[13]. Other triazoles find many synthetic uses as halogenating agents[1] or as activating polymeric reagents[14]. Now-a-days, 1,2,4-triazole derivatives are

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widely used as biocides[15] and as antifungal agents[16]. Many 1,2,4-triazole derivatives find applications as photographic reagents[1].

In the present work, a new set of 1,2,4-triazole derivatives were prepared from the reaction of C-acetyl and C-ester nitrilimines with benzoyl-, ethoxycarbonyl- and acetyl-hydrazones of acyclic, cyclic and heterocyclic ketones.

EXPERIMENTAL

Melting points were determined on Electrothermal Mel. Temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared spectrometer (KBr discs). ^1H 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 spectrometers at 70 eV. Hydrazonoyl halides[9] (**1**), hydrazones[17] (**2–4**) were prepared as previously described.

Synthesis of Substituted Heterocyclic Spiro Compounds (5–7)

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 (**2–4**) (0.02 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:

4-Benzoylamino-1-(4-chlorophenyl)-4,5-dihydro-3-methoxycarbonyl-5,5-dimethyl-1H-1,2,4-triazole (5a)

Yield (67%), m.p. = 186°C, ^1H NMR: 10.2 (s, 1H, NH), 7.2–8.9 (m, 9H, aromatic protons), 3.8 (s, 3H, CH_3O), 1.6 (s, 6H, $2CH_3$ at C5); ^{13}C NMR: 168.3 (NC=O), 158.47 (CH_3OC=O), 89.13 (C-5 carbon), 51.92 (OCH_3), 25.0 ($2CH_3$ at C5), IR (cm^{-1}) 3345 ν(NH), 1703 ν(CH_3OC=O), 1682 ν(PhC=O).

hrms m.w.: found 386.114476, calcd. 386.114568, mass difference for $C_{19}H_{19}ClN_4O_3$ = 0.24.

4-Benzoylamino-1-(4-chlorophenyl)-3-methoxycarbonyl-1,2,4-triazaspiro[4.4]non-2-ene (5b)

Yield (87%); m.p. = 195–196°C, ^1H NMR: 10.5 (s, 1H, NH), 7.3–8.1 (m, 9H, aromatic protons), 4.0 (s, 2H, OCH_3), 1.9–2.4 (m, 8H, cyclopentane protons); ^{13}C NMR: 173.2 (NC=O), 163.3 (CH_3OC=O), 102.3 (C-5 ring spiro carbon), 56.7 (OCH_3); IR (cm^{-1}) 3264 ν(NH), 1731 ν(CH_3OC=O), 1673 ν(PhC=O).

hrms m.w.: found 412.129995, calcd. 412.130218, mass difference for $C_{21}H_{21}ClN_4O_3$ = 0.54.

4-Benzoylamino-1-(4-chlorophenyl)-3-methoxycarbonyl-1,2,4-triazaspiro[4.5]dec-2-ene (5c)

Yield (75%); m.p. = 175–176°C, ^{1}H NMR: 10.5 (s, 1H, NH), 7.3–8.1 (m, 9H, aromatic protons), 4.0 (s, 3H, OCH_3), 1.4–2.1 (m, 10H, cyclohexane protons); ^{13}C NMR: 168.2 (NC=O), 159.7 (CH_3OC=O), 88.0 (C-5 ring spiro carbon), 52.1 (OCH_3); IR (cm^{-1}) 3351 ν(NH), 1697 ν(CH_3OC=O), 1673 ν(PhC=O).

hrms m.w.: found 426.145431, calcd. 426.145868, mass difference for $C_{22}H_{23}ClN_4O_3$ = 1.02

4-Benzoylamino-1-(4-chlorophenyl)-3-methoxycarbonyl-1,2,4-triazaspiro-[4.6]undec-2-ene (5d)

Yield (72%); m.p. = 181–182°C, ^{1}H NMR: 10.1 (s, 1H, NH), 7.4–8.0 (m, 9H, aromatic protons), 4.0 (s, 3H, OCH_3), 1.6–2.4 (m, 12H, cycloheptane protons); ^{13}C NMR: 173.3 (NC=O), 163.7 (CH_3OC=O), 97.78 (C-5 ring spiro carbon), 56.7 (OCH_3); IR (cm^{-1}) 3318 ν(NH), 1698 ν(CH_3OC=O), 1689 ν(PhC=O).

hrms (M Wt: found 440.161881, calcd. 440.161518, mass difference for $C_{23}H_{25}ClN_4O_3$ = –.83

1-(4-Chlorophenyl)-4-ethoxycarbonylamino-3-methoxycarbonyl-1,2,4-triazaspiro[4.4]non-2-ene (6b)

Yield (40%); m.p. = 149–150°C, ^{1}H NMR: 7.0–7.2 (m, 4H, aromatic protons), 6.6 (s, 1H, NH), 4.2 (q, 2H, OCH_2), 3.8 (s, 3H, OCH_3), 1.6–2.2 (m, 8H, cyclopentane protons), 1.2 (t, 3H, CH_3); ^{13}C NMR: 158.5 (CH_3OC=O), 156.8 (NC=O), 97.0 (C-5 ring spiro carbon), 62.10 (OCH_2), 52.2 (OCH_3), 14.1 (CH_3); IR (cm^{-1}) 3258 ν(NH), 1734 ν(CH_3OC=O), 1720 ν(PhC=O).

hrms m.w.: found 380.124860, calcd. 380.125133, mass difference for $C_{17}H_{21}ClN_4O_4$ = 0.72.

1-(4-Chlorophenyl)-4-ethoxycarbonylamino-3-methoxycarbonyl-1,2,4-triazaspiro[4.5]dec-2-ene (6c)

Yield (55%); m.p. = 156–158°C, ^{1}H NMR: 7.1–7.3 (m, 4H, aromatic protons), 6.6 (s, 1H, NH), 4.2 (q, 2H, OCH_2), 3.8 (s, 3H, OCH_3), 1.5–2.2 (m, 10H, cyclohexane protons), 1.3 (t, 3H, CH_3); ^{13}C NMR: 159.5 (CH_3OC=O), 156.4 (NC=O), 89.1 (C-5 ring spiro carbon), 61.7 (OCH_2), 52.1 (OCH_3), 14.1 (CH_3); IR (cm^{-1}) 3298 ν(NH), 1744 ν(CH_3OC=O), 1711 ν(PhC=O).

hrms m.w.: found 394.141149, calcd. 394.140783, mass difference for $C_{18}H_{23}ClN_4O_4$ = –0.93.

1-(4-Chlorophenyl)-4-ethoxycarbonylamino-3-methoxycarbonyl-1,2,4-triazaspiro[4.6]undec-2-ene (6d)

Yield (54%); m.p. = 103–104°C, ^{1}H NMR: 7.1–7.3 (m, 4H, aromatic protons), 6.7 (s, 1H, NH), 4.2 (q, 2H, OCH_2), 3.8 (s, 3H, OCH_3), 1.5–2.3 (m, 12H, cycloheptane protons), 1.2 (t, 3H, CH_3); ^{13}C NMR: 159.8 (CH_3OC=O), 156.6 (NC=O), 96.1 (C-5 ring spiro carbon), 62.0 (OCH_2), 52.2 (OCH_3), 14.1 (CH_3); IR (cm^{-1}) 3256 ν(NH), 1732 ν(CH_3OC=O), 1722 ν(PhC=O).

hrms m.w.: found 408.156113, calcd. 408.156433, mass difference for $C_{19}H_{25}ClN_4O_4$ = 0.79.

1-(4-Chlorophenyl)-4-ethoxycarbonylamino-3-methoxycarbonyl-8-oxa-1,2,4-triazaspiro[4.5]dec-2-ene (6e)

Yield (55%); m.p. = 160–162°C, ^{1}H NMR: 7.2–7.4 (m, 4H, aromatic protons), 6.7 (s, 1H, NH), 4.2 (q, 2H, OCH_2), 3.9 (s, 3H, OCH_3), 3.7–4.04 (m, 4H, tetrahydropyran OCH_2 protons) 1.8–2.2 (m, 4H, tetrahydropyran, CH_2 protons), 1.2 (t, 3H, CH_3); ^{13}C NMR: 158.7 (CH_3OC=O), 156.4 (NC=O), 84.5 (C-5 ring spiro carbon), 67.5 (OCH_2 of the ring) 62.0 (OCH_2), 52.3 (OCH_3), 14.1 (CH_3); IR (cm^{-1}) 3250 ν(NH), 1732 ν(CH_3OC=O), 1720 ν(PhC=O).

hrms m.w: found 396.119729, calcd. 396.120048, mass difference for $C_{17}H_{21}ClN_4O_5$ = 0.81.

1-(4-Chlorophenyl)-4-ethoxycarbonylamino-3-methoxycarbonyl-8-methyl-1,2,4-triazaspiro[4.5]dec-2-ene (6f)

Yield (52%); m.p. = 103–104°C, ^{1}H NMR: 8.5 (s, 1H, NH), 7.0–7.2 (m, 4H, aromatic protons), 4.2 (q, 2H, OCH_2), 3.8 (s, 3H, OCH_3), 1.5–2.2 (m, 9H, cyclohexane protons), 1.3 (t, 3H, CH_3) 1.0 (d, 3H, CH_3 at cyclohexane); ^{13}C NMR: 160.0 (CH_3OC=O), 156.5 (NC=O), 89.0 (C-5 ring spiro carbon), 61.2 (OCH_2), 52.2 (OCH_3), 30.7 (CH_3 at cyclohexane), 14.0 (CH_3); IR (cm^{-1}) = 3304 ν(NH), 1721 ν(CH_3OC=O), 1717 ν(PhC=O).

hrms m.w.: found 408.156066, calcd. 408.156433, mass difference for $C_{19}H_{25}ClN_4O_4$ = 0.90.

8-tert-Butyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-3-methoxycarbonyl-1,2,4-triazaspiro[4.5]dec-2-ene (6g)

Yield (70%); m.p. = 128–129°C, ^{1}H NMR: 9.0 (s, 1H, NH), 7.8–8.1 (m, 4H, aromatic protons), 4.2 (q, 2H, OCH_2), 3.8 (s, 3H, OCH_3), 1.3–2.2 (m, 9H, cyclohexane protons), 1.3 (t, 3H, CH_3) 0.9 (s, 9H, tert-butyl group at cyclohexane); ^{13}C NMR: 158.0 (CH_3OC=O), 155.5 (NC=O), 89.0 (C-5 ring spiro carbon), 61.7 (OCH_2), 52.2 (OCH_3), 45.8, 41.1, 32.4, 27.5, 22.4 (tert-butylcyclohexane carbons), 14.9 (CH_3); IR cm^{-1} 3294 (NH), 1744 (CH_3OC=O), 1722 (PhC=O).

hrms m.w.: found 450.203227, calcd. 450.203383, mass difference for $C_{22}H_{31}ClN_4O_4$ = 0.34.

1-(4-Chlorophenyl)-4-ethoxycarbonylamino-3-methoxycarbonyl-9,12-dioxa-1,2,4-triazaspiro[4.2.4.2]tetradec-2-ene (6h)

Yield (75%); m.p. = 146–148°C, ^{1}H NMR: 8.8 (s, 1H, NH), 7.1–7.3 (m, 4H, aromatic protons), 4.2 (q, 2H, OCH_2), 3.9 (s, 4H, OCH_2 of the ring), 3.8 (s, 3H, OCH_3), 1.6–2.5 (m, 8H, cyclohexane protons), 1.3 (t, 3H, CH_3); ^{13}C NMR: 159.0 (CH_3OC=O), 156.5 (NC=O), 107.1 (spiro carbon, C-8), 87.0 (C-5 ring spiro carbon), 64.1, 63.9 (OCH_2 of the ring), 62.1 (OCH_2), 52.1 (OCH_3), 14.1 (CH_3); IR (cm^{-1}) 3259 ν(NH), 1733 ν(CH_3OC=O), 1720 ν(PhC=O).

hrms m.w.: found 452.146567, calcd. 452.146263, mass difference for $C_{20}H_{25}ClN_4O_6$ = –0.67.

1-(4-Chlorophenyl)-8-ethoxycarbonyl-4-ethoxycarbonylamino-3-methoxycarbonyl-1,2,4,8-tetraazaspiro[4.5]dec-2-ene (6i)

Yield (42%); m.p. = 141–142°C, ^{1}H NMR: 7.8 (s, 1H, NH), 7.1–8.3 (m, 4H, aromatic protons), 4.2, 4.1 (2q, 2H, OCH_2), 3.9 (s, 3H, OCH_3), 1.8–2.2 (m, 8H, cyclohexane protons), 1.3, 1.2 (2t, 3H, CH_3); ^{13}C NMR: 159.0 (CH_3OC=O), 156.6 (NC=O), 94.0 (C-5 ring spiro carbon), 61.7, 61.1 (2OCH_2), 52.2 (OCH_3), 14.3,14.2 (2CH_3).

hrms m.w.: found 467.157009, calcd. 467.157161, mass difference for $C_{20}H_{26}ClN_5O_6$ = 0.33.

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

Yield (40%); m.p. = 181–182°C, ^{1}H NMR: 8.0 (s, 1H, NH), 7.1–7.3 (m, 4H, aromatic protons), 2.5 (s, 3H, CH_3), 1.7–2.2 (m, 8H, cyclopentane protons); ^{13}C NMR: 188.0 (CH_3C=O), 172.0 (NC=O), 97.9 (C-5 ring spiro carbon), 26.3 (CH_3C=O); IR (cm^{-1}) 3305 ν(NH), 1685 ν(CH_3C=O), 1668 ν(NC=O); $M^{+\cdot}$ = 336/338 for $C_{16}H_{21}ClN_4O_2$

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

Yield (30%); m.p. = 197–199°C, ^{1}H NMR: 8.9 (s, 1H, NH), 7.1–7.2 (m, 4H, aromatic protons), 2.5 (s, 3H, CH_3), 1.2–2.2 (m, 10H, cyclohexane protons); ^{13}C NMR: 190.0/188.9 (CH_3C=O), 177.6/171.5 (NC=O), 88.9/88.8 (C-5 ring spiro carbon), 26.3/25.9 (CH_3C=O); IR (cm^{-1}) 3326 ν(NH), 1684 ν(CH_3C=O), 1668 ν(NC=O); $M^{+\cdot}$ = 350/352 for $C_{17}H_{23}ClN_4O_2$

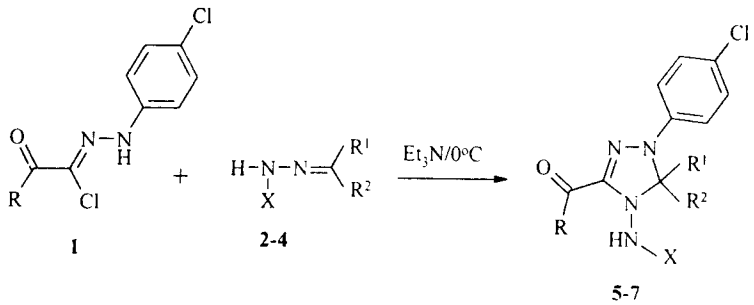
3-Acetyl-4-acetylamino-1-(4-chlorophenyl)-1,2,4-triazaspiro[4.6]undec-2-ene (7d)

Yield (25%); m.p. = 159–160°C, ^{1}H NMR: 8.1 (s, 1H, NH), 7.1–7.2 (m, 4H, aromatic protons), 2.5 (s, 3H, CH_3), 1.5–2.3 (m, 12H, cycloheptane protons); ^{13}C NMR: 188.0 (CH_3C=O), 174 (NC=O), 87.0 (C-5 ring spiro carbon), 25.6 (CH_3C=O); IR (cm^{-1}) 3351 ν(NH), 1685 ν(CH_3C=O), 1673 ν(NC=O); $M^{+\cdot}$ = 364/366 for $C_{18}H_{25}ClN_4O_2$

RESULTS AND DISCUSSION

The reaction of hydrazonoyl halides (**1**) (precursors of nitrilimines) with substituted hydrazones (**2–4**) was conducted in THF at room temperature in presence of triethylamine for 24 h in a 1 : 1.2 mol ratio. Yellow products (**5–7**) were obtained after work-up of the reaction mixtures as indicated in the experimental section (Table-1, **Scheme-1**)

Structural assignment of the resulting products was based on spectral data. Thus, on the IR spectra, one N—H and two C=O stretching frequencies were observed for these products .

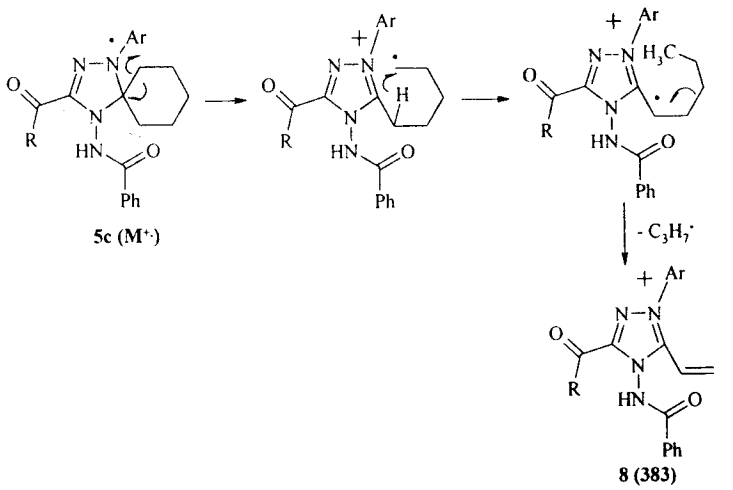


Scheme-1

TABLE-1
PHYSICAL DATA AND MOLECULAR ION PEAKS FOR COMPOUNDS (5–7)

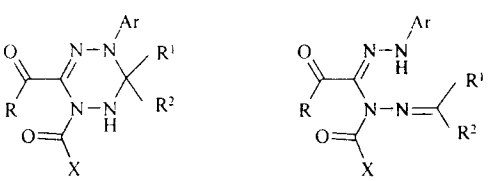
Compd.	R	m.p. (°C)	Yield (%)	m.f.	$M^{+\bullet}$
5a	CH_3O	186–188	67	$C_{19}H_{19}ClN_4O_3$	386/388
5b	CH_3O	195–196	87	$C_{21}H_{21}ClN_4O_3$	412/414
5c	CH_3O	175–176	75	$C_{22}H_{23}ClN_4O_3$	426/428
5d	CH_3O	181–182	72	$C_{23}H_{25}ClN_4O_3$	440/442
6b	CH_3O	149–150	40	$C_{17}H_{21}ClN_4O_4$	380/382
6c	CH_3O	156–158	55	$C_{18}H_{23}ClN_4O_4$	394/396
6d	CH_3O	103–104	54	$C_{19}H_{25}ClN_4O_4$	408/410
6e	CH_3O	160–162	55	$C_{17}H_{21}ClN_4O_5$	396/398
6f	CH_3O	103–104	52	$C_{19}H_{25}ClN_4O_4$	408/410
6g	CH_3O	128–129	70	$C_{22}H_{31}ClN_4O_4$	450/452
6h	CH_3O	146–148	75	$C_{20}H_{25}ClN_4O_6$	452/454
6i	CH_3O	141–142	42	$C_{20}H_{26}ClN_5O_6$	467/469
7b	CH_3	181–182	40	$C_{16}H_{21}ClN_4O_2$	336/338
7c	CH_3	197–199	30	$C_{17}H_{23}ClN_4O_2$	350/352
7d	CH_3	159–160	25	$C_{18}H_{23}ClN_4O_2$	362/364

The mass spectra and hrms display peaks for the correct molecular ions. The base peak of compound (**5a**) occurs at 371/373 which results from α-cleavage of the methyl group at the ring. The base peak for compounds (**6b–d**) at 383 is that of the vinyl triazole cation (**8**) resulting from α-cleavage of the carbocyclic ring followed by H-migration and subsequent C—C homolysis. **Scheme-2** shows the fragmentation pattern for compound (**5c**) as an example. This fragmentation pattern is well known in the literature for cycloalkanone fragmentation[18]. Similar fragmentation pattern is also observed for compounds (**5**) with a base peak at 351.



Scheme-2

1H- and ^{13}C NMR of these compounds show the signals consistent with the suggested structure. Of special importance is the signal of the spiro carbon of the triazoline ring which rules out the cyclocondensation of six-membered tetrazine ring (**9**) or the acyclic adducts (**10**). Spiro carbons of tetrazines like (**9**) appears about 70 ppm[8]. The detailed NMR data of these compounds are presented in the experimental part. Tests for antifungal and antibacterial activities of these compounds will be done later.



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