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2,6-Diaryl-4,4-Disubstituted 1,4-Dihydropyridines: Source for Spiro Heterocycles

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ABSTRACT: *Novel spiro heterocycles (***5–12***) were obtained by the cyclocondensation of 2,6-diaryl-4,4-dimethoxycarbonyl-/4-cyano-4-ethoxycarbonyl-1,4-dihydropyridines (***3/4***) with hydrazine hydrate, hydroxylamine hydrochloride, urea, and thiourea. All the compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectral data.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:513–517, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10183

INTRODUCTION

Doping of heteroatoms within the carbon framework has been considered as a versatile method to design new heterocycles. In this perspective attempts are made to incorporate nitrogen into 3,3-disubstituted 1,5-diaryl-1,5-pentanediones [1] to furnish 4,4-disubstituted 2,6-diaryl-1,4-dihydropyridines (**3/4**). Indeed dihydropyridine and its derivatives were used in the treatment of cardiovascular diseases such as angina, hypertension, or arrhythmia [2]. On the other hand 1,4-dihydropyridine fused to a carbocyclic ring exhibited calcium modulatory properties [3,4]. On the basis of this, it was thought to develop spiro heterocycles from 1,4-dihydropyridines. In fact remarkable progress has been made by our group during the last one decade in the synthesis of spiro heterocycles [5], which was traditionally associated with the presence of *gem* diester or cyano ester functionality in the molecule and this has become the basis for the present communication. Thus, this report includes hitherto unknown spiro heterocycles from 4,4-disubstituted 1,4-dihydropyridines.

RESULTS AND DISCUSSION

The synthesis involves the reaction of 1,5-diaryl-3,3-dimethoxycarbonyl-1,5-pentanediones (**1a–c**)/1,5-diaryl-3-cyano-3-ethoxycarbonyl-1,5-pentanediones (**2a–c**) with ammonium acetate in acetic acid under reflux conditions to give 2,6-diaryl-4,4-dimethoxycarbonyl-1,4-dihydropyridines (**3a-c**)/2,6-diaryl-4-cyano-4-ethoxycarbonyl-1,4-dihydropyridines (**4a–c**) [6]. The *gem*-dicarboxylate or *gem*-cyano ester on condensation with hydrazine hydrate, hydroxylamine hydrochloride, urea, and thiourea would furnish pyrazole, isoxazole, pyrimidine, and thiopyrimidine derivartives. Accordingly, treatment of **3a–c** with these reagents in the presence of NaOMe resulted in the formation of 7,9-diaryl-2,3,8-triaza-spiro[4.5]deca-6,9-diene-1,4-diones (**5a–c**), 7,9-diaryl-2-oxo-3,8-diaza-spiro[4.5]deca-6,9-diene-

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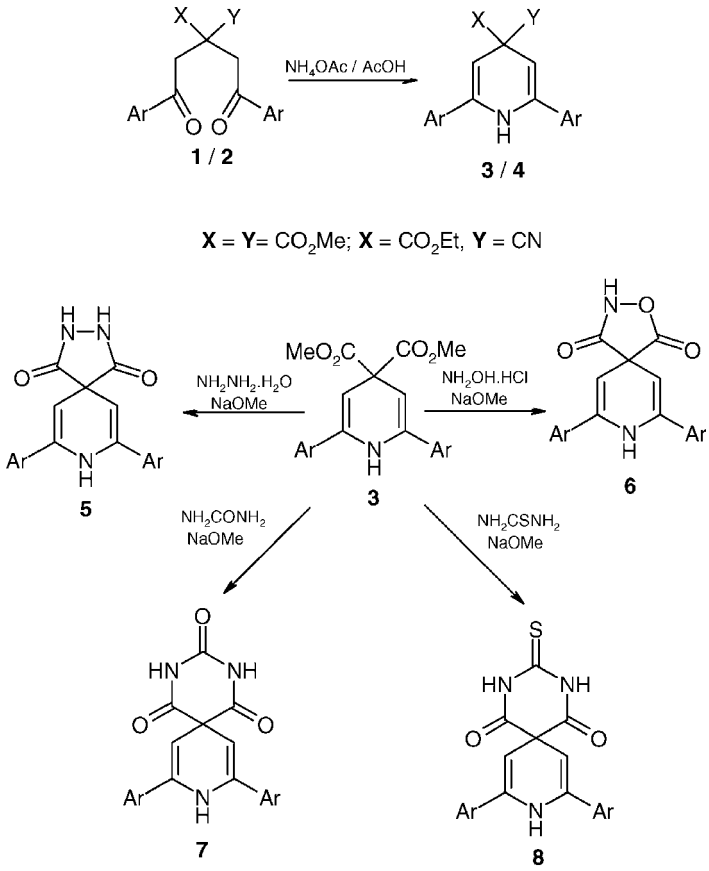
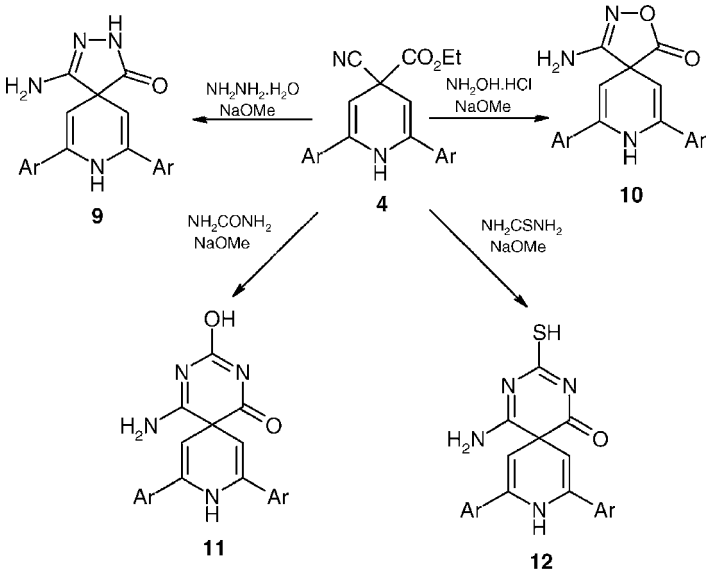


SCHEME 1



SCHEME 2

1,4-diones (**6a–c**), 8,10-diaryl-2,4,9-triaza-spiro-[5.5]undeca-7,10-diene-1,3,5-triones (**7a–c**), and 8, 10-diarly-3-thioxo-2,4,9-triaza-spiro[5.5]undeca-7, 10-diene-1,5-diones (**8a–c**), respectively (Scheme 1). In a similar way, the reaction of **4a–c** gave 4-amino-7,9-diaryl-2,3,8-triaza-spiro[4.5]deca-3,6,-9-trien-1-ones (**9a–c**), 4-amino-7,9-diaryl-2-oxo-3,8-diaza-spiro[4.5] deca-3,6,9-trien-1-ones (**10a–c**), 5-amino-3-hydroxy-8,10-diaryl-2,4,9-triaza-spiro-[5.5]undeca-2,4,7,10-tetraen-1-ones (**11a–c**), and 5-amino-3-mercapto-8,10-diaryl-2,4,9-triaza-spiro-[5.5]undeca-2,4,7,10-tetraen-1-ones (**12a–c**), respectively (Scheme 2, Table 1).

The IR spectra of **5–8** exhibited absorption bands in the regions 1645–1682, 3200–3470, and 1495–1510 cm^{-1} for CO, NH, and C=S of pyrazolidinedione/isoxazolidinedione/pyrimidinetrione/thioxopyrimidinedione moiety. The compounds **9–12** showed absorption bands in the regions 1685–1710 and 3240–3470 cm^{-1} for CO, OH and NH_2 and NH of aminopyrazolone/aminoisoxazolone/aminopyrimidine/thioxo-pyrimidine moiety. Apart from these, **6** and **10** exhibited bands around 1725–1735 cm^{-1} for CO—O of isoxazole moiety. In the ^1H NMR spectra the methine protons C_6—H and C_{10}—H in **5, 6, 9, 10** and C_7—H and C_{11}—H in **7, 8, 11, 12** showed a sharp singlet in the region $\delta = 4.85–5.63$. The NH in **5–8** displayed a broad singlet at $\delta = 6.19–10.68$. However, a broad singlet observed around $\delta = 6.89–10.14$ in **9–12** accounts for NH and NH_2. Apart from these, **11** showed a singlet for OH at $\delta = 6.89–6.97$ while **12** for SH at $\delta = 1.37–1.43$ (Table 2). The signals for NH_2, NH, and OH disappeared on deuteration. The structure of **5–12** were also confirmed by ^{13}C NMR spectra (Table 2).

EXPERIMENTAL

Melting points were determined on Mel-Temp apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 1600 FT-IR spectrometer using KBr disc. The wave numbers are given in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 operating at 300 MHz and 75.45 MHz, respectively, on a Bruker spectrospin spectrometer with TMS as an internal standard. Purity of the compounds was checked by TLC using silica gel 'G' (BDH) and hexane–ethyl acetate (3:1) as eluents. The elemental analyses were obtained from Micro Analytical Laboratory, University of Pune, Pune, India.

TABLE 1 Physical Data of Compounds **5–12**

	mp (°C)	*Yield (%)*	*Mol. Formula (Mol. Wt.)*	*Found[a] (%)*		
				C	*H*	*N*
5a	237–239	72	$C_{19}H_{15}N_3O_2$ (317.35)	71.80 (71.91)	4.82 (4.76)	13.39 (13.24)
5b	233–235	64	$C_{21}H_{19}N_3O_4$ (377.40)	66.98 (66.83)	5.00 (5.07)	11.08 (11.13)
5c	224–226	66	$C_{19}H_{13}Cl_2N_3O_2$ (386.24)	59.00 (59.09)	3.48 (3.39)	11.02 (10.88)
6a	194–196	62	$C_{19}H_{14}N_2O_3$ (318.34)	71.48 (71.69)	4.34 (4.43)	8.94 (8.80)
6b	202–204	68	$C_{21}H_{18}N_2O_4$ (378.39)	66.82 (66.66)	4.85 (4.79)	7.30 (7.40)
6c	183–184	73	$C_{19}H_{12}Cl_2N_2O_3$ (387.23)	58.80 (58.94)	3.08 (3.12)	7.36 (7.23)
7a	275–277	69	$C_{20}H_{15}N_3O_3$ (345.36)	69.72 (69.56)	4.34 (4.38)	12.31 (12.17)
7b	284–285	57	$C_{22}H_{19}N_3O_5$ (405.41)	65.36 (65.18)	4.81 (4.72)	10.20 (10.36)
7c	270–271	60	$C_{20}H_{13}Cl_2N_3O_3$ (414.25)	57.90 (57.99)	3.10 (3.16)	10.26 (10.14)
8a	280–282	68	$C_{20}H_{15}N_3O_2S$ (361.43)	66.67 (66.47)	4.10 (4.18)	11.78 (11.63)
8b	276–277	62	$C_{22}H_{19}N_3O_4S$ (421.48)	62.83 (62.69)	4.60 (4.54)	10.11 (9.97)
8c	269–271	63	$C_{20}H_{13}Cl_2N_3O_2S$ (430.32)	55.71 (55.82)	3.00 (3.05)	9.64 (9.76)
9a	207–209	61	$C_{19}H_{16}N_4O$ (316.37)	72.25 (72.14)	5.07 (5.10)	17.85 (17.71)
9b	225–227	58	$C_{21}H_{20}N_4O_3$ (376.42)	67.11 (67.01)	5.40 (5.36)	14.81 (14.88)
9c	199–201	65	$C_{19}H_{14}Cl_2N_4O$ (385.26)	59.15 (59.24)	3.69 (3.66)	14.61 (14.54)
10a	189–191	70	$C_{19}H_{15}N_3O_2$ (317.35)	72.11 (71.91)	4.71 (4.76)	13.40 (13.24)
10b	195–197	66	$C_{21}H_{19}N_3O_4$ (377.40)	66.68 (66.83)	5.12 (5.07)	11.22 (11.13)
10c	176–177	69	$C_{19}H_{13}Cl_2N_3O_2$ (386.24)	59.22 (59.09)	3.43 (3.39)	10.69 (10.88)
11a	263–265	62	$C_{20}H_{16}N_4O_2$ (344.38)	69.92 (69.76)	4.76 (4.68)	16.40 (16.27)
11b	281–283	68	$C_{22}H_{20}N_4O_4$ (404.43)	65.50 (65.34)	4.94 (4.98)	14.00 (13.85)
11c	273–274	71	$C_{20}H_{14}Cl_2N_4O_2$ (413.27)	58.01 (58.13)	3.46 (3.41)	13.44 (13.56)
12a	260–262	60	$C_{20}H_{16}N_4OS$ (360.44)	66.55 (66.65)	4.52 (4.47)	15.68 (15.54)
12b	256–258	59	$C_{22}H_{20}N_4O_3S$ (420.49)	62.90 (62.84)	4.85 (4.79)	13.47 (13.32)
12c	277–279	62	$C_{20}H_{14}Cl_2N_4OS$ (429.33)	55.84 (55.95)	3.37 (3.29)	12.98 (13.05)

[a]Values in parentheses indicate calculated values.

TABLE 2 Spectroscopic Data of Compounds **5–12**

	δ ^{1}H NMR	δ ^{13}C NMR
5a	4.95 (s, 2H, C_6 & C_{10}—H), 7.22–7.78 (m, 10H, ArH), 8.24 (bs, 3H, NH—NH, NH).	45.12 (C_5), 117.28 (C_6 & C_{10}), 137.95 (C_7 & C9), 175.80 (C1 & C4).
5b	3.65 (s, 6H, Ar—OCH_3), 4.92 (s, 2H, C_6 & C_{10}—H), 7.24–7.75 (m, 8H, ArH), 8.62 (bs, 3H, NH—NH, NH).	–
5c	4.99 (s, 2H, C_6 & C_{10}—H), 7.21–7.77 (m, 8H, ArH), 8.76 (bs, 3H, NH—NH, NH).	45.06 (C_5), 117.26 (C_6 & C_{10}), 137.11 (C_7 & C_9), 175.70 (C_1 & C_4).
6a	5.11 (s, 2H, C_6 & C_{10}—H), 7.27–7.78 (m, 10H, ArH), 9.32 (bs, 2H, NH—O, NH).	54.84 (C_5), 114.78 (C_6 & C_{10}), 140.97 (C_7 & C_9), 176.73, 175.93 (C_1 & C_4).
6b	3.63 (s, 6H, Ar—OCH_3), 5.19 (s, 2H, C_6 & C_{10}—H), 7.30–7.82 (m, 8H, ArH), 9.39 (bs, 2H, NH—O, NH).	–
6c	4.98 (s, 2H, C_6 & C_{10}—H), 7.29–7.80 (m, 8H, ArH), 9.25 (bs, 2H, —NH—O, NH).	54.76 (C_5), 114.28 (C_6 & C_{10}), 140.95 (C_7 & C_9), 176.69, 175.94 (C_1 & C_4).
7a	4.98 (s, 2H, C_7 & C_{11}—H), 6.32 (s, 1H, NH), 7.32–7.81 (m, 10H, ArH), 10.11 (bs, 2H, —NH—CO—NH—).	42.78 (C_6), 118.23 (C_7 & C_{11}), 137.94 (C_8 & C_{10}), 151.64 (C_3), 164.35 (C_1 & C_5).
7b	3.62 (s, 6H, Ar—OCH_3), 4.95 (s, 2H, C_7 & C_{11}—H), 6.36 (s, 1H, NH) 7.34–7.85 (m, 8H, ArH), 10.44 (bs, 2H, —NH—CO—NH).	–
7c	4.91 (s, 2H, C_7 & C_{11}—H), 6.59 (s, 1H, NH), 7.33–7.84 (m, 8H, ArH), 10.12 (bs, 2H, —NH—CO—NH).	–
8a	4.85 (s, 2H, C_7 & C_{11}—H), 6.24 (s, 1H, NH), 7.27–7.79 (m, 10H, ArH), 10.59 (bs, 2H, —NH—CS—NH).	41.58 (C_6), 113.48 (C_7 & C_{11}), 137.25 (C_8 & C_{10}), 159.92 (C_1 & C_5), 170.27 (C_3).
8b	3.61 (s, 6H, Ar—OCH_3), 4.91 (s, 2H, C_7 & C_{11}—H), 6.19 (s, 1H, NH), 7.23–7.79 (m, 8H, ArH), 10.87 (bs, 2H, —NH—CS—NH).	–
8c	5.11 (s, 2H, C_7 & C_{11}—H), 6.27 (s, 1H, NH), 7.29–7.78 (m, 8H, ArH), 10.68 (bs, 2H, —NH—CS—NH).	41.74 (C_6), 113.92 (C_7 & C_{11}), 137.99 (C_8 & C_{10}), 159.87 (C_1 & C_5), 170.31 (C_3).
9a	5.29 (s, 2H, C_6 & C_{10}—H), 7.25–7.78 (m, 10H, ArH), 8.64–8.66 (bs, 3H, NH_2, NH), 10.02 (s, 1H, —NH—N).	39.12 (C_5), 109.29 (C_6 & C_{10}), 135.76 (C_7 & C_9), 162.92 (C_4), 175.48 (C_1).
9b	3.59 (s, 6H, Ar—OCH_3), 5.27 (s, 2H, C_6 & C_{10}—H), 7.26–7.77 (m, 8H, ArH), 8.59–8.61 (bs 3H, NH_2, NH), 9.98 (s, 1H, NH—N).	–
9c	5.32 (s, 2H, C_6 & C_{10}—H), 7.24–7.80 (m, 8H, ArH), 8.61–8.63 (bs, 3H, NH_2, NH), 10.14 (s, 1H, —NH—N).	41.29 (C_5), 109.95 (C_6 & C_{10}), 137.98 (C_7 & C_9), 163.29 (C_4), 175.82 (C_1).
10a	5.63 (s, 2H, C_6 & C_{10}—H), 7.24–7.79 (m, 10H, ArH), 8.58–8.60 (bs, 3H, NH_2, NH).	49.93 (C_5), 108.27 (C_6 & C_{10}), 138.10 (C_7 & C_9), 177.24 (C_4), 175.54 (C_1).
10b	3.61 (s, 6H, Ar—OCH_3), 5.62 (s, 2H, C_6 & C_{10}—H), 7.25–7.80 (m, 8H, ArH), 8.46–8.48 (bs, 3H, NH_2, NH).	–
10c	5.58 (s, 2H, C_6 & C_{10}—H), 7.23–7.79 (m, 8H, ArH), 8.59–8.61 (bs, 3H, NH_2, NH).	49.71 (C_5), 108.88 (C_6 & C_{10}), 138.46 (C_7 & C_9), 177.84 (C_4), 175.39 (C_1).
11a	5.51 (s, 2H, C_7 & C_{11}—H), 6.89–6.91 (bs, 4H, NH, NH_2, OH), 7.22–7.76 (m, 10H, ArH).	37.24 (C_6), 107.55 (C_7 & C_{11}), 135.41 (C_8 & C_{10}), 163.02 (C_3), 179.43 (C_1), 185.18 (C_5).
11b	3.58 (s, 6H, Ar—OCH_3), 5.58 (s, 2H, C_7 & C_{11}—H), 6.92–6.93 (bs, 4H, NH, NH_2, OH), 7.24–7.79 (m, 8H, ArH).	–
11c	5.59 (s, 2H, C_7 & C_{11}—H), 6.95–6.97 (s, 4H, NH, NH_2, OH), 7.23–7.77 (m, 8H, ArH).	37.19 (C_6), 107.14 (C_7 & C_{11}), 135.21 (C_8 & C_{10}), 163.42 (C_3), 179.01 (C_1), 185.61 (C_5).
12a	1.39 (s, 1H, SH), 5.60 (s, 2H, C_7 & C_{11}—H), 7.23–7.75 (m, 10H, ArH), 8.78–8.80 (bs, 3H, NH, NH_2).	37.27 (C_6), 107.19 (C_7 & C_{11}), 136.08 (C_8 & C_{10}), 175.67 (C_3), 176.29 (C_1), 180.47 (C_5).
12b	1.43 (s, 1H, SH), 3.60 (s, 6H, Ar—OCH_3), 5.57 (s, 2H, C_7 & C_{11}—H), 7.24–7.78 (m, 8H, ArH), 8.69–8.71 (bs, 3H, NH, NH_2).	–
12c	1.37 (s, 1H, SH), 5.62 (s, 2H, C_7 & C_{11}—H), 7.23–7.78 (m, 8H, ArH), 8.68–8.70 (bs, 3H, NH, NH_2).	38.05 (C_6), 105.25 (C_7 & C_{11}), 143.20 (C_8 & C_{10}), 175.39 (C_3), 175.95 (C_1), 180.45 (C_5).

*2,6-Diaryl-4,4-dimethoxycarbonyl-1,4-dihydropyridine (**3a–c**)/2,6-Diaryl-4-cyano-4-ethoxycarbonyl-1,4-dihydropyridine (**4a–c**)*

Compound **1/2** (10 mmol), was dissolved in AcOH (20 ml). To this NH_4OAc (1.5 g) was added and refluxed for 2 h. The reaction mixture was cooled and poured onto crushed ice. The product obtained was recrystallized from methanol.

*7,9-Diaryl-2,3,8-triaza-spiro[4.5]deca-6,9-diene-1,4-dione (**5a–c**)/7,9-Diaryl-2-oxo-3,8-diaza-spiro[4.5]deca-6,9-diene-1,4-dione (**6a–c**)/8,10-Diaryl-2,4,9-triaza-spiro[5.5]undeca-7,10-diene-1,3,5-trione (**7a–c**)/8,10-Diaryl-3-thioxo-2,4,9-triaza-spiro[5.5]undeca-7,10-diene-1,5-dione (**8a–c**)*

A mixture of **3** (10 mmol), 80% hydrazine hydrate (15 mmol)/hydroxylamine hydrochloride

(10 mmol)/urea (10 mmol)/thiourea (10 mmol), methanol (25 mL), and 10% NaOMe (5 ml) was refluxed for 5–6 h, cooled, and poured onto crushed ice containing HCl. The product obtained was recrystallized from methanol.

*4-Amino-7,9-diaryl-2,3,8-triaza-spiro[4.5]deca-3,6,9-trien-1-one (***9a–c***)/4-Amino-7,9-diaryl-2-oxo-3,8-diaza-spiro[4.5]deca-3,6,9-trien-1-one (***10a–c***)/5-Amino-3-hydroxy-8,10-diaryl-2,4,9-triaza-spiro[5.5]undeca-2,4,7,10-tetraen-1-one (***11a–c***)/5-Amino-3-mercapto-8,10-diaryl-2,4,9-triaza-spiro[5.5]undeca-2,4,7,10-tetraen-1-one (***12a–c***)*

To a solution of **4** (10 mmol) in ethanol (25 mL), 80% hydrazine hydrate (15 mmol)/hydroxylamine hydrochloride (10 mmol)/urea (10 mmol)/thiourea (10 mmol), and 10% NaOEt (5 ml) was added. The contents were refluxed for 5–8 h, cooled, and poured onto crushed ice and acidified with acetic acid. The separated solid was filtered and recrystallized from ethanol.

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