HETEROCYCLES, Vol. 31, No. 1, 1990

STUDIES ON DIPOLAR CYCLOADDITION REACTIONS. SYNTHESIS OF 3,4-DISUBSTITUTED 1-(2,4-DICHLOROBENZAMIDOYL)AZETIDIN-2-ONES AND FUSED Δ^2-PYRAZOLINES

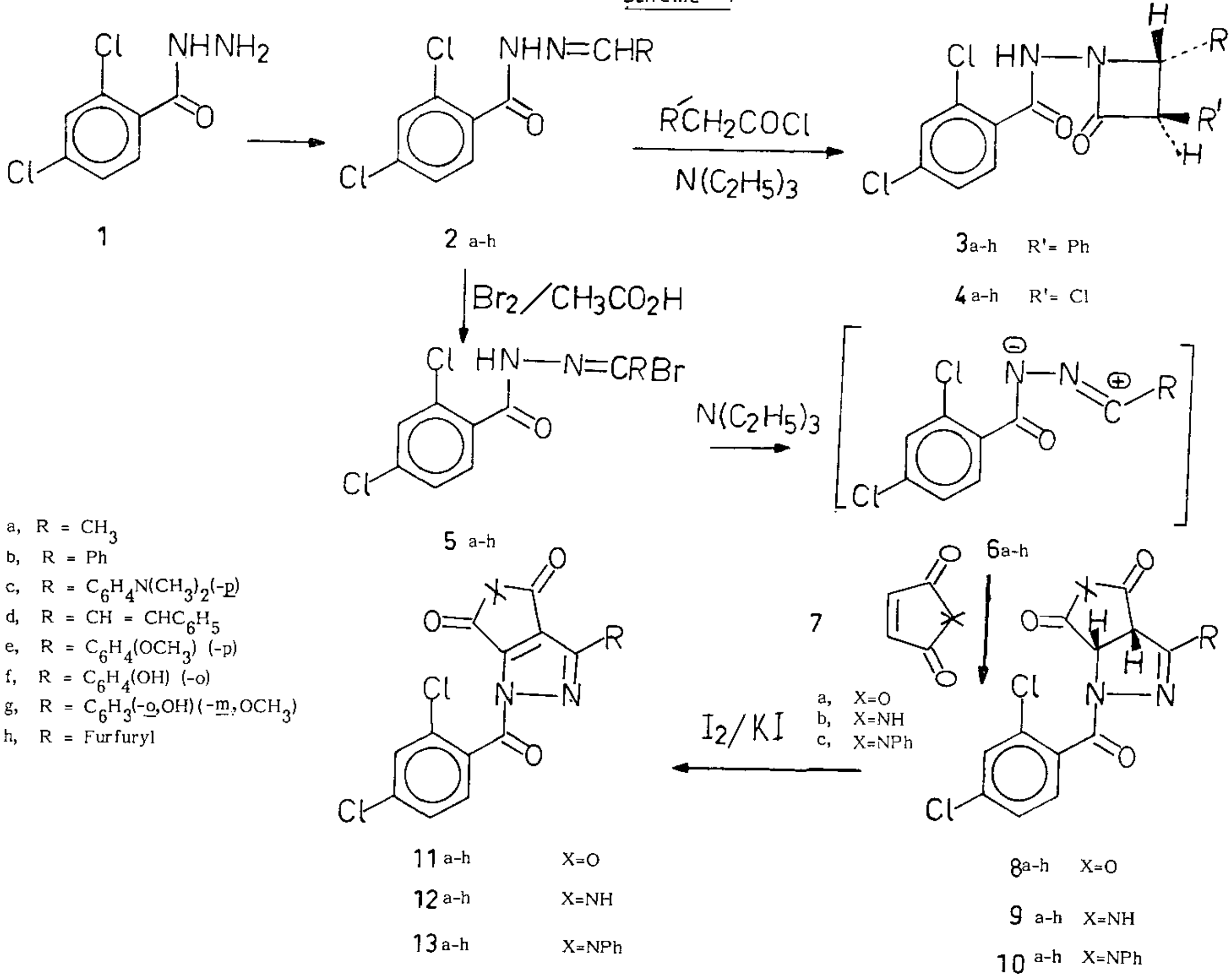
Chandra Sekhar Sarma, Probin C. Gogoi, and Jibon C. S. Kataky*
Regional Research Laboratory, Jorhat 785 006, Assam, INDIA

Abstract - From the dipolar cycloaddition reactions of ketenes and anils 2, the new azetidinones 3 and 4 were isolated. In addition the reaction between the nitrilimine 6 and cyclic olefins 7 gave new fused Δ^2-pyrazolines 8, 9 and 10. The chemical behaviour and spectral data of the new compounds were determined.

Because of our interest[1] in the chemistry of oxadiazoles, thiadiazoles, triazoles, oxadiazole thiones, azetidinones and thiadiazolidinones, we have published the results of our study in these fields[1a-g] and established the dipolar cyclocondensation of mercaptoacetic acid on the anils of biologically active compounds such as 2,4-dichlorophenylhydrazide, 2-aminooxadiazoles and thiadiazoles.[1f,g] In recent years cycloaddition chemistry has made a significant impact in organic synthesis and contributed much in the synthesis of complex natural products.[2a] Early developments in the cycloaddition reaction have been mainly reported by Huisgen et al.[3] Nitrilimines have been known to react with various types of monosubstituted olefins to give predominantly 5-substituted 2-pyrazolines (8,9,10).[3a] On the other hand, considerably a few reactions[2b] between nitrilimines and cyclic olefinic dipolarophiles have been investigated. Our interest in the chemistry of heterocycles[1] and the results obtained from these studies prompted us to investigate the dipolar cycloaddition reactions of ketenes generated from monochloroacetyl chloride, phenylacetyl chloride to anils (2) and nitrilimines (6) generated from hydrazidoyl bromide (5) to cyclic olefinic dipolarophiles and to investigate these cycloadducts. Exploration of the studies is principally directed towards the synthesis of new heterocyclic products. The results obtained during this attempt are reported in this paper.

The compound 1 underwent facile condensation with aliphatic and aromatic aldehydes in absolute ethanol in the presence of acetic acid as catalyst giving 2,4-dichlorobenzoylhydrazone (2) in quantitative yield.[1f] The hydrazones (2a-h) on condensation with monochloroacetyl chloride in dry dioxane in the presence of triethylamine produce 4-alkyl/aryl/aralkyl-3-phenyl-1-(2,4-dichlorobenzamidoyl)azetidin-2-ones (3a-h) having the established stereochemistry[4] (Scheme 1). Apparently, this cycloaddition proceeds via a ketene intermediate following [2+2]cycloaddition as reported earlier.[5]

Scheme 1



a, R = CH_3
b, R = Ph
c, R = $C_6H_4N(CH_3)_2$(-p)
d, R = CH = CHC_6H_5
e, R = $C_6H_4(OCH_3)$ (-p)
f, R = $C_6H_4(OH)$ (-o)
g, R = C_6H_3(-o,OH)(-m,OCH_3)
h, R = Furfuryl

The 1,3-dipolar cycloaddition reactions of cyclic olefinic dipolarophiles (7a-c) to nitrilimines (6a-h), prepared in situ from the corresponding N-aroylhydrazidoyl bromide (5a-h) in benzene in the presence of triethylamine, were performed. Lack of stabilizing factors, and sensitivity towards atmospheric component were the major factors which precluded the isolation of these nitrilimines and therefore, these species generated in solution and undergo cycloaddition with dipolarophiles in situ.[6] The reactions of nitrilimines (6a-h) with olefinic dipolarophiles were carried out in equimolar amounts to give Δ^2-pyrazolines (8a-h, 9a-h, 10a-h) exclusively in 60-80% yield (Scheme 1).

The structures of the compounds newly synthesized were deduced on the basis of analytical and spectral data (Tables 1 and 2). The regiochemistry of the cycloadducts 8 was established by a comparison of the nmr shifts of the 3-CH and 4-CH protons with those in literature.[7] The chemical shifts observed at δ 3.30 and 3.70(s) corresponds well with the reported value[7] (δ 3.27 and 3.83 respectively).

In the ir spectra the azetidinones (3a-h) and (4a-h) showed the bands ν cm^{-1}) 1780-1730 (C=O) characteristic for ß-lactam structure and 1675-1630 (CONH). The ^{1}H nmr spectra of azetidinones 3,4 showed peaks at δ4.60-4.90 and 5.30-5.90 (d, methine-H). The compounds 8,9,10 showed the bands (ν cm^{-1}) at 1780-1760 in the ir spectra. The ^{1}H nmr spectra of 8,9,10 showed peaks at δ 3.20-3.50 and 3.60-3.80 as singlet for H-C_7 and H-C_8 which are the characteristic protons. These two protons disappear in the ^{1}H nmr when the compounds were oxidised with iodine in potassium iodide (I_2/KI)[8] to give compounds 11,12 and 13.

EXPERIMENTAL

Melting points were determined with a Büchi Oil heated apparatus in open capillaries and are uncorrected. Infrared (ir) spectra were recorded with a Perkin-Elmer 237B spectrophotometer using potassium bromide discs, unless otherwise stated (ν max in cm^{-1}). Nuclear magnetic resonance (^{1}H nmr) spectra were recorded in solutions stated with TMS as the internal reference in 60 MHz on a Varian T-60 spectrometer (chemical shifts in δ ppm) and mass spectra were recorded on an AEIMS-30 instrument at 70 ev. 2,4-Dichlorobenzhydrazine (1) was prepared from ethyl 2,4-dichlorobenzoate following the method of Yale et al.[9] 1-(2,4-Dichlorobenzoyl)hydrazones (2a-h) were prepared from hydrazine (1) and corresponding aldehydes following the reported method.[1f]

4-Alkyl/aryl/aralkyl-3-phenyl-1-(2,4-dichlorobenzamidoyl)azetidin-2-ones 3a-h

General Procedure :

To a well stirred solution of hydrazone 2 (0.01 mol) and triethylamine (0.01 mol) in dry dioxane(100 ml) was added monochloroacetyl chloride (0.02 mol) dropwise at room temperature, the mixture was stirred for another 5 h and then the reaction mixture was cooled to room temperature. Triethylamine hydrochloride was filtered and solvent was removed under reduced pressure to get crude product which on recrystallization from C_2H_5OH gave (3a-h), ir 1780-1730(C=O) and 1675-1650(-CONH), ^1H nmr(acetone-d_6) δ 4.60-4.90 and 5.30-5.90 (d, methine -H protons). The physical data of the compounds are given in Table 1. All the compounds gave satisfactory microanalyses and the data are given in Table 1.

4-Alkyl/aryl/aralkyl-3-chloro-1-(2,4-dichlorobenzamidoyl)azetidin-2-ones 4a-h

Compounds 4a-h were prepared as above using phenylacetyl chloride instead of chloroacetyl chloride.

N-(2,4-Dichlorobenzoyl)hydrazidoyl bromide 5a-h

General Procedure[10]

To a stirred solution of hydrazone 2 (0.01 mol) in glacial acetic acid (75 ml) was added dropwise a solution of bromine (0.01 mol) in 25 ml of acetic acid with stirring. The mixture is stirred for 3 h and the solid was then filtered, washed with ether and dried in air. Sometimes reaction mixture was poured into crushed ice and the solid was filtered, washed with ether and dried. The compounds were characterised on the basis of spectroscopic data.

1-(2,4-Dichlorobenzoyl)furo[3,2-c]pyrazolin-4,6-diones 8a-h

General Procedure

To a solution of hydrazidoyl bromide 5 (0.0012 mol) and maleic anhydride (7a) (0.001 mol) in 15 ml of dry benzene, triethylamine (0.0002 mol) was added slowly with stirring. The mixture was then refluxed for 20 h. Benzene solution was washed 4 times with water, and dried over anhydrous sodium sulfate. Benzene was then removed under reduced pressure. The solid thus obtained was recrystallised from C_2H_5OH to get compounds 8a-h. Ir 1780-1760(C=O), ^1H nmr δ 3.20-3.50 and 3.60-3.80 (s, H-C_7 and H-C_8 respectively). The physical data of the compounds are given in Table 2. Compounds 9 and 10 were prepared similarly using maleimide and N-phenylmaleimide (7b,7c) respectively instead of maleic anhydride (7a). All the compounds gave satisfactory microanalyses and the data are given in Table 2.

1-(2,4-Dichlorobenzoylfuro[3,2-c]pyrazole-4,6-diones 11,12,13

General Procedure

To a solution of 8 (1 mmol) in 10% aq. sodium hydroxide solution (25 ml) was added a solution of iodine (2 g), potassium iodide (14 g) in water (10 ml) dropwise with constant stirring for 2 h. The dark brown solid thus obtained was filtered and recrystallised from C_2H_5OH to furnish the compound 11 (yield 30%). Few of the compounds are obtained by acidifying the reaction mixtures with ice cooled conc. hydrochloric acid.

Compounds 12 and 13 are also obtained following the similar procedure mentioned above.

These compounds showed ir (ν max cm^{-1}) at 1650-1630 (C=C=C=O). The two ^1H nmr peaks at δ3.20 and 3.60 were disappeared.

Table 1

Spectroscopic data of 4-alkyl/aryl/aralkyl-3-(phenyl or chloro)-1-(2,4-dichlorobenzamidoyl)azetidin-2-ones (3a-h, 4a-h)

Compd No	R R'=Ph or Cl	mp (°C)	Yield (%)	ir(KBr) ν cm^{-1} C=O	^{1}H-nmr (δ ppm, acetone-d_6)	Analysis(%) Found C	H	N	Calcd C	H	N
3a	CH_3	131	65	1760	4.60(d, J=1Hz), 5.40(d, J=1Hz)	58.52	4.25	8.12	58.46	4.01	8.02
3b	C_6H_5	145	75	1770	4.80(d, J=1Hz), 5.50(d, J=1Hz)	64.34	3.83	6.88	64.24	3.89	6.81
3d	$CH=CH-C_6H_5$	140	65	1775	4.70(d, J=1Hz), 5.40(d, J=1Hz)	65.89	4.15	6.48	65.91	4.12	6.41
3e	$C_6H_4(OCH_3)(-\underline{p})$	135	70	1750	4.80(d, J=1Hz), 5.30(d, J=1Hz)	62.69	4.03	6.39	62.59	4.08	6.35
3f	$C_6H_4(OH)(-\underline{o})$	136	75	1740	4.50(d, J=1Hz), 5.70(d, J=1Hz)	61.90	3.72	6.68	61.84	3.75	6.56
3g	$C_6H_3(\underline{o}-OH)(\underline{m}-OCH_3)$	180	55	1730	4.60(d, J=1Hz), 5.40(d, J=1Hz)	60.58	3.85	6.25	60.41	3.94	6.13
3h	Furfuryl	183	60	1780	4.90(d, J=1Hz), 5.70(d, J=1Hz)	62.30	3.62	7.39	62.35	3.64	7.27
4a	CH_3	125	65	1765	4.50(d, J=1Hz), 5.50(d, J=1Hz)	42.82	2.90	9.25	42.94	2.93	9.11
4b	C_6H_5	150	75	1775	4.90(d, J=1Hz), 5.70(d, J=1Hz)	51.90	2.93	7.56	51.98	2.98	7.58
4d	$CH=CH-C_6H_5$	145	60	1755	4.70(d, J-1Hz), 5.50(d, J=1Hz)	54.75	3.38	7.20	54.63	3.29	7.08
4e	$C_6H_4(OCH_3)(-\underline{p})$	182	90	1745	4.80(d, J=1Hz), 5.50(d, J=1Hz)	51.19	3.30	7.18	51.08	3.25	7.01
4f	$C_6H_4(OH)(-\underline{o})$	154	68	1750	4.90(d, J=1Hz), 5.80(d, J=1Hz)	49.78	2.78	7.35	49.82	2.85	7.27
4g	$C_6H_3(\underline{o}-OH)(\underline{m}-OCH_3)$	115	55	1730	4.70(d, J=1Hz), 5.40(d, J=1Hz)	49.20	3.22	6.69	49.11	3.13	6.74
4h	Furfuryl	185	79	1775	4.50(d, J=1Hz), 5.80(d, J=1Hz)	46.81	2.58	7.85	46.74	2.50	7.79

Table 2

Spectral data of compounds 8, 9 and 10

Compd No	R	mp (°C)	Yield (%)	ir(KBr) ν cm^{-1} C=O	^{1}H nmr (δ ppm, DMSO-d_6)	Analysis (%) Found (Calcd) C	H	N
	X = O							
8a	CH_3	Gummy	40	1730	3.32(s, 1H)	47.63	2.40	8.65
				1690	3.70(s, 1H)	(47.72	2.45	8.57)
8b	C_6H_5	129	60	1735	3.40(s, 1H)	55.69	2.50	7.29
				1700	3.80(s, 1H)	(55.54	2.57	7.20)
8c	$C_6H_4N(CH_3)_2$(-p)	153	55	1735	3.35(s, 1H)	55.68	3.55	9.70
				1685	3.70(s, 1H)	(55.57	3.47	9.72)
8d	CH=CH-C_6H_5	120	35	1730	3.25(s, 1H)	57.80	2.93	6.68
				1685	3.68(s, 1H)	(57.85	2.89	6.75)
8e	$C_6H_4(OCH_3)$(-p)	182	38	1735	3.30(s, 1H)	54.49	2.80	6.71
				1690	3.80(s, 1H)	(54.45	2.86	6.68)
8f	$C_6H_4(OH)$(-o)	192	42	1725	3.35(s, 1H)	53.48	2.52	6.85
				1695	3.70(s, 1H)	(53.35	2.47	6.92)
8g	C_6H_3(o-OH)(m-OCH_3)	185	52	1740	3.30(s, 1H)	52.43	2.71	6.48
				1690	3.65(s, 1H)	(52.43	2.76	6.44)
8h	Furfuryl	173	40	1725	3.20(s, 1H)	50.72	2.20	7.46
				1680	3.75(s, 1H)	(50.67	2.11	7.39)
	X= NH							
9a	CH_3	Gummy	39	1710	3.25(s, 1H)	47.80	2.81	12.93
				1650	3.70(s, 1H)	(47.87	2.76	12.89)
9b	C_6H_5	154	45	1700	3.30(s, 1H)	55.73	2.92	10.95
				1655	3.70(s, 1H)	(55.68	2.84	10.83)
9c	$C_6H_4N(CH_3)_2$(-p)	201	61	1720	3.27(s, 1H)	55.75	3.68	12.85
				1680	3.80(s, 1H)	(55.69	3.71	12.99)
9d	CH=CH-C_6H_5	198	42	1730	3.30(s, 1H)	57.85	3.20	10.20
				1660	3.85(s, 1H)	(57.99	3.14	10.15)
9e	$C_6H_4(OCH_3)$(-p)	158	50	1720	3.25(s, 1H)	54.50	3.20	10.21
				1665	3.75(s, 1H)	(54.56	3.11	10.05)
9f	$C_6H_4(OH)$(-o)	169	64	1725	3.30(s, 1H)	53.55	2.78	10.45
				1655	3.85(s, 1H)	(53.48	2.72	10.39)
9g	C_6H_3(o-OH)(m-OCH_3)	185	72	1730	3.25(s, 1H)	52.69	2.88	9.73
				1655	3.70(s, 1H)	(52.55	2.99	9.68)
9h	Furfuryl	175	38	1720	3.30(s, 1H)	50.95	2.45	11.21
				1670	3.80(s, 1H)	(50.81	2.38	11.11)
	X = N-Ph							
10a	CH_3	158	42	1720	3.25(s, 1H)	56.85	3.31	10.52
				1640	3.80(s, 1H)	(56.73	3.23	10.45)
10b	C_6H_5	169	53	1710	3.35(s, 1H)	62.19	3.20	9.12
				1660	3.75(s, 1H)	(62.08	3.23	9.05)
10c	$C_6H_4N(CH_3)_2$(-p)	210	56	1725	3.28(s, 1H)	61.61	3.82	11.13
				1685	3.85(s, 1H)	(61.55	3.95	11.05)
10d	CH=CH-C_6H_5	205	61	1730	3.30(s, 1H)	63.72	3.51	8.62
				1670	3.75(s, 1H)	(63.69	3.47	8.57)
10e	$C_6H_4(OCH_3)$(-p)	194	62	1720	3.30(s, 1H)	60.71	3.52	8.63
				1670	3.80(s, 1H)	(60.74	3.44	8.50)
10f	$C_6H_4(OH)$(-o)	185	65	1730	3.25(s, 1H)	60.15	3.20	8.80
				1660	3.75(s, 1H)	(60.01	3.13	8.75)
10g	C_6H_3(o-OH)(m-OCH_3)	191	71	1725	3.30(s, 1H)	58.89	3.41	8.29
				1650	3.85(s, 1H)	(58.84	3.33	8.24)
10h	Furfuryl	173	60	1710	3.25(s, 1H)	58.20	2.93	9.31
				1660	3.85(s, 1H)	(58.16	2.86	9.25)

ACKNOWLEDGEMENT

The authors are grateful to Dr J. N. Baruah, Director, Regional Research Laboratory, Jorhat, Assam, for permitting one of the authors (PG) to carry out the research work in the laboratory. One of us (CSS) is also grateful to CSIR, New Delhi, for the award of Junior Research Fellowship. We thank the Analytical Chemistry Division of this laboratory for some of the spectral analysis.

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Received, 3rd July, 1989