Synthesis and Some Reactions of 3,5-Diaryl Cyclohex-2-ene-6-(1`,2`,4`-Triazol-5`-yl-3`-Thioxo)-1-one

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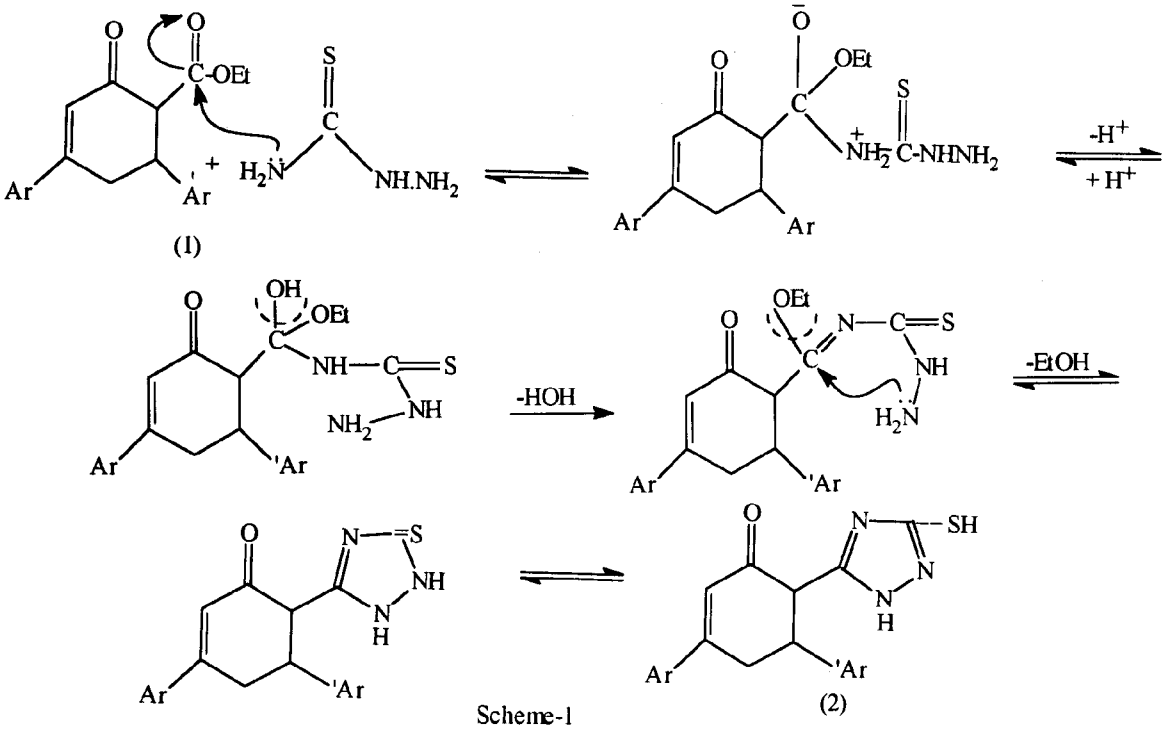
Summary: 6-carbethoxy-3,5-diaryl cyclohex-2-enone (1) was condensed with thiosemicarbazide in boiling pyridine to give 2 which reacted with some electrophiles and nucleophiles to give substituted cyclohexenones.

Introduction

The chemistry of cyclohexenones has been extensively studied and efficient methods were developed for their synthesis [1-3]. The aim of the present work is to synthesize some new cyclohexenones incorporated with nitrogen and sulphur moieties of possible biological activity. Thus, ineraction of 6-carboethoxy-3,5-diaryl cyclohex-2-enone (1) with thiosemicarbazide in boiling pyridine afforded 3,5-diaryl cyclohex-2-ene-6-(1`,2`,4`-triazol-5`-yl-3`-thioxo)-1-one (2). The synthetic pathway could be considered as nucleophilic attack of the amino group at the carbonyl of the cyclohexenone ring followed by cyclization [4] (Scheme 1).

The presence of the thione $\rightleftharpoons$ thiol dynamic equilibrium in compound (2) was detected from its ir and ^{1}H-NMR spectra and from the study of the following reactions.

Alkylation of 2 using methyl iodide in alcoholic sodium hydroxide yielded 3,5-diaryl cyclohex-2-ene-6-(1`,3`-dimethyl mercapto-1`,2`, 4`-triazol-5`-yl)-1-one (3). Also, alkylation of 2 using ethyl chloroacetate in boiling dry acetone containing anhydrous potassium carbonate gave 3,5-diarylcyclohex-2-ene-6-(3`-ethoxycarbonyl methylmercapto-1`,2`,4`-triazol-5`-yl)-1-one (4). The ester derivative (4) reacted with primary



Scheme-1

amines namely, aniline, *p*-chloroaniline, and/or benzylamine in boiling ethanol to give the amide derivatives (**5a-c**).

This work also investigated the reaction of **2** with acrylonitrile [5] in boiling ethanol containing anhydrous sodium carbonate to give 3,5-diaryl cyclohex-2-ene-6-[3`-(2-cyanoethylthio)-1,2,4-triazol-5-yl]-1-one (**6**). Compound (**2**) reacted with primary amines namely, benzylamine, aniline, and/or *p*-toluidine in boiling ethanol to give the corresponding 3,5-diaryl cyclohex-2-ene-6-(3`-amino)1`,2`,4`-triazol-5`-yl)-1-ones (**7a-c**). In the same manner, the reaction of **2** with hydrazine hydrate afforded the corresponding hydrazino derivative (**7d**). The reaction takes its pathway via nucleophilic attack at the thione group only.

The hydrazino derivative (**7d**) readily condensed with aromatic aldehydes namely, benzaldehyde, anisaldehyde, and/or *p*-chlorobenzaldehyde in boiling ethanol to give the corresponding arylidenehydrazonyl derivatives (**8a-c**).

Reaction of **7d** with acetylacetone in boiling ethanol afforded 3,5-diaryl cyclohex-2-ene-6-[3`-(3,5-dimethylpyrazol-5-yl)-1`,2`,4`-triazol-5`-yl]-1-one (**9**). On the other hand, compound (**7d**) reacted as a nucleophile with ethyl chloroacetate in boiling ethanol to give **10** (Scheme-2).

Biological screening

The prepared compounds were tested against different types of Gram positive, Gram negative, unicellular yeast, and filamentous fungi using agar-diffusion technique [6], and/or agar-plate diffusion technique [7]. Compound (**2**), (**3**), (**5**) and (**8**) had antibacterial activity against Gram negative bacteria *serratia sp., E. coli,* and *P. aeruginosa* at 500 ppm concentration level. Compound (**2**), (**4**), (**8**), (**9**) and (**10**) had antifungal activity against multicelluler fungi at concentration of 500 ppm. The other compounds did not show any antibacterial or antifungal activities, cf. Table 2.

Experimental

Physical data and microanalytical results are listed in Table 1. Melting points are uncorrected. The ir spectra are measured on PYE Unicam SP 200G spectrophotometer using KBr Wafer technique. The ^{1}H-NMR spectra are recorded on a Varian EM 60 instrument using TMS as an internal standard.

3,5-Diaryl cyclohex-2-ene-6-(1`,2`,4`-triazol-5`-yl-3`-thioxo)-1-one (2)

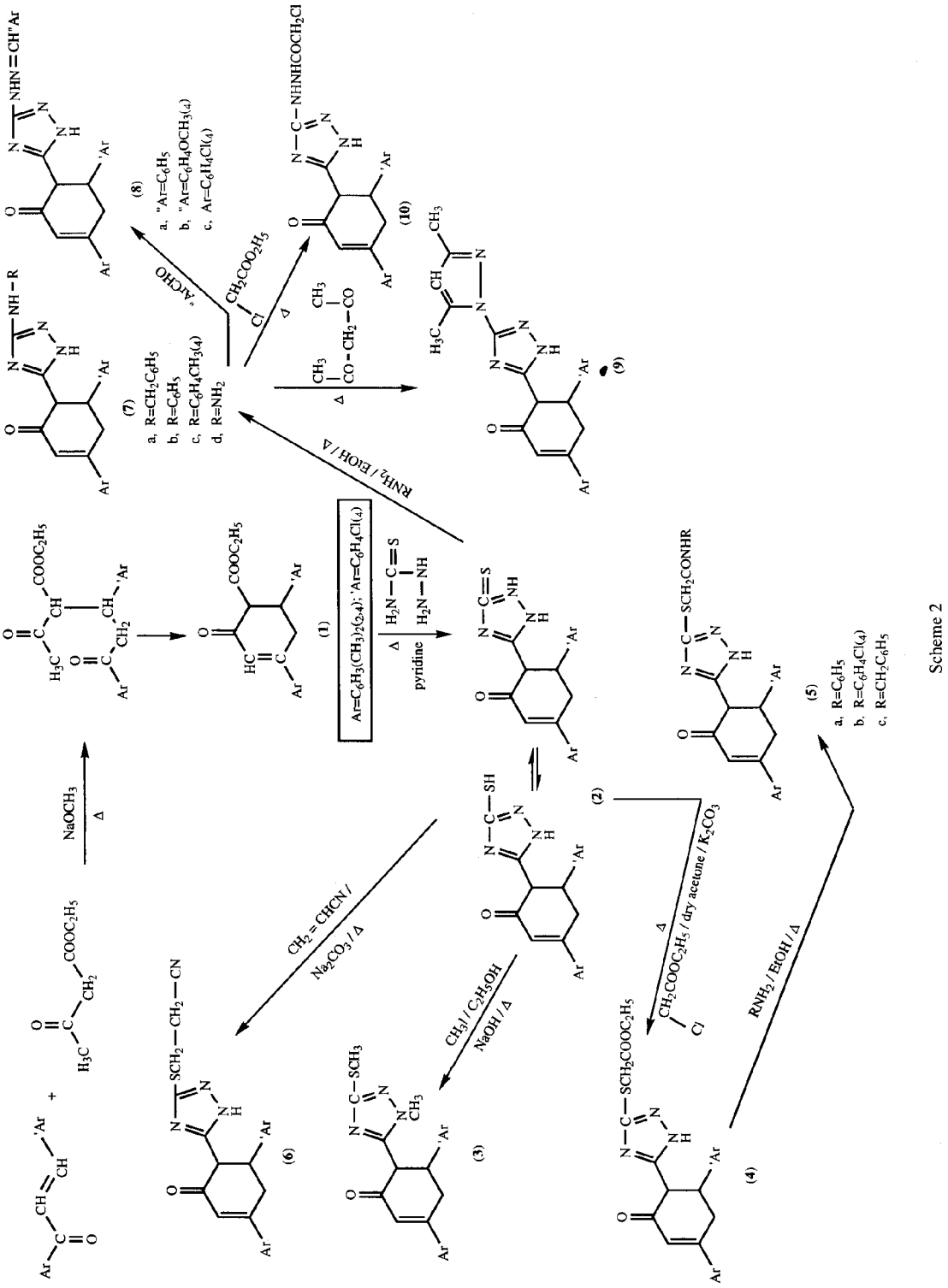
A mixture of 6-carbethoxy-3,5-diaryl cyclohex-2-ene-1-one (**1**) (0.01 mol) and thiosemicarbazide (0.01 mol) in 30 ml of pyridine was refluxed for 6 hr. It was then poured into ice/10% HCl and the product that separated was collected, washed well with water and recrystallised from ethanol to give **2**. IR (KBr; ν, cm^{-1}); 3240-3180 (ν NH), 2570 (ν SH), 1695 (ν C=O), 1630 (ν C=N), and 1240 (ν C=S). ^{1}H-NMR (DMSO-d_6; δ, ppm): 2.3 (s, 3H, Ar-CH_3), 2.45 (s, 3H, Ar-CH_3), 4.1 (d, 1H, -CH), 4.6 (d, 1H, -CH), 5.9 (s, 1H, -CH), 7.6 (m, 7H, Ar-H), 9.6 (br, 1H, -SH), 10.3 and 11.5 (br, 2H, of NH and NH-C=S).

Alkylation of compound 2 with methyl iodide. Formation of 3.

A mixture of compound **2** (0.01 mol) and methyl iodide (0.01 mol) in 10 ml of ethanol containing 10 ml of aqueous NaOH (20%) was refluxed for 24 hr. After cooling, the reaction mixture was poured into ice-10% HCl, then extracted with ether. The residue left after evaporation of the ethereal layer was triturated with light petrol (b.p. 60-80°C), then recyrstallised from ethanol to give **3**. IR (KBr; ν, cm^{-1}); 1695 (ν C=O), 1620 (ν C=N) and devoid of any absorption bands due to ν C=S or ν SH, ^{1}H-NMR ($CDCl_3$; δ, ppm): 1.25, 2.2 and 2.4 (3 x s, 9H, 2 x Ar-CH_3 and N-CH_3) 3.2 (s, 3H, -S-CH_3), 6.8-8.8 (m, 7H, Ar-H) and 10.4 (br, 1H, cyclic NH).

Alkylation of compound 2 with ethyl chlolroacetate. Fornmation of 4.

A mixture of compound **2** (0.01 mol) and ethyl chloroacetate (0.015 mol) in 50 ml of dry acetone containing anhydrous potassium carbonate (0.04 mol) was refluxed for 24 h. After concentration, the reaction mixture was filtered off while hot onto water and the solid product was coollectd, washed well and recrystallised from ethanol give **4**. IR (ν, cm^{-1}); 3320-3180 (νNH, broad), 1710 and 1690 (two νC=O) and 1620 (ν C=N). ^{1}H-NMR ($CDCl_3$: , ppm): 2.2 (s, 3H, Ar-CH_3), 2.3 (s, 3H, Ar-CH_3), 3.6 (t, J=7 Hz, 3H, -CH_2-CH_3), 4.15 (q, J=7 Hz, 2H, -CH_2CH_3), 6.85-



Scheme 2

Table-1: Physical data of the prepared compounds (2-10).

Comp. No.	mp°c solvent*	Yield %	Mol.formula	Analysis Calcd./Found % C	H	N	S	Cl
2	168 EtOH	79	$C_{22}H_{20}N_3OSCl$	64.46 64.5	4.88 4.9	10.25 10.3	7.81 7.8	8.66 8.7
3	141 EtOH	45	$C_{24}H_{24}N_3OSCl$	65.82 65.8	5.48 5.5	9.60 9.6	7.31 7.3	8.11 8.2
4	157 EtOH	62	$C_{26}H_{26}N_3O_3SCl$	62.96 63.0	5.24 5.3	8.47 8.5	6.45 6.5	7.16 7.2
5a	202 EtOH	82	$C_{30}H_{27}N_4O_2SCl$	66.35 66.4	4.97 4.9	10.32 10.4	5.89 5.9	6.54 6.6
5b	235 EtOH	75	$C_{30}H_{26}N_4O_2SCl_2$	62.39 62.4	4.506 4.5	9.705 9.8	5.54 5.6	12.305 12.4
5c	245 EtOH	90	$C_{31}H_{29}N_4O_2SCl$	66.84 66.9	5.21 5.3	10.06 10.1	5.75 5.8	6.37 6.4
6	152 P.E.	35	$C_{25}H_{23}N_4OSCl$	64.86 64.9	4.97 5.0	12.108 12.2	6.91 6.9	7.67 7.7
7a	132 P.E.	45	$C_{29}H_{27}N_4OCl$	72.12 72.2	5.59 5.6	11.606 11.6		7.35 7.4
7b	141 EtOH	52	$C_{28}H_{25}N_4OCl$	71.71 71.7	5.33 5.4	11.95 12.0		7.57 7.6
7c	173 EtOH	60	$C_{29}H_{27}N_4OCl$	72.12 72.1	5.59 5.6	11.606 11.6		7.35 7.4
7d	101 *n*-H	34	$C_{22}H_{22}N_5OCl$	64.78 64.8	5.39 5.4	17.17 17.2		8.71 8.7
8a	129 *n*-H	67	$C_{29}H_{26}N_5OCl$	70.23 70.3	5.24 5.2	14.12 14.1		7.16 7.2
8b	197 BuOH	60	$C_{30}H_{28}N_5O_2Cl$	68.506 68.5	5.32 5.3	13.32 13.4		5.67 5.7
8c	160 EtOH	53	$C_{29}H_{25}N_5OCl_2$	65.66 65.7	4.71 4.8	13.207 13.2		13.39 13.4
9	212 EtOH	41	$C_{27}H_{26}N_5OCl$	68.71 68.8	5.51 5.6	14.84 14.9		7.52 7.6
10	231 EtOH	55	$C_{24}H_{23}N_5O_2Cl_2$	59.504 59.5	4.75 4.8	14.46 14.5		14.66 14.7

*Where P.E. = petroleum ether (b.p. 100-120°C; *n*-H = *n*-hexane).

Table 2: The antimicrobial activity of used compounds. (+++ = maximum activity, ++ = moderate activity, + = slight activity and - = inactive).

Test organisms	2	3	4	5	8	9	10
Bacillus megaterium							
Bacillus cereus	+	+		+	+	+	+
Staphyllococcus aureus							
Escherichia coli	++	++		+++	++		
Pseudomonas aeruginosa	+++	++		+++	+++		
Serratia marcescens	+++	+		+++	+++		
Candida albicans							
Penicillium chrysogenum	+		++		+++	+++	++
Fusarium oxysporium	++		+		++	++	++
Aspergillus fumigatus	++		++		++	++	+
Mucor psillius	+++		++		++	++	++

8.35 (m, 7H, Ar-H) and 11.8 (br, exchangeable with D_2O, 1H, -NH).

Reaction of the mercaptoester derivatives 4 with primary amines. Formation of the amide derivatives (5a-c).

A mixture of compound 4 (0.01 mol) and the primary amine namely, aniline, 4-chloroaniline, and/or benzylamine (0.01 mol) in 30 ml of absolute ethanol was refluxed for 6h. After concentration and cooling, the product that separated was collected, and recrystallised from ethanol to give **5a-c**. IR (KBr; cm^{-1}); 3320-3210 (ν NH, broad). 1695 (ν C=O), 1665 (ν C=O, of amide), 1620 (ν C=N). **5a** ^{1}H-NMR (DMSO-d_6; δ, ppm): 2.25 (s, 3H, Ar-CH_3), 2.35 (s, 3H, Ar-CH_3), 3.75 (s, 2H, C-SCH_2-), 5.9 (s, 1H, -CH-), 6.8-8.9 (m, 12H, Ar-H) and 11.3 (br, 1H, D_2O exchangeable, -NH).

Reaction of compound 2 with acrylonitrile. Formation of the S-cyanoethyl derivative (6).

A mixture of **2** (0.01 mol) and acrylonitrile (0.01 mol) in 30 ml of ethanol containing

anhydrous sodium carbonate (0.02 mol) was refluxed for 6 h. After cooling, the reaction mixture was filtered onto ice-10% HCl and the solid product was collected, washed well and recrystallised from light petrol (bp. 100 - 120°C) to give **6**. IR (KBr; ν, cm^{-1}); 3220-3180 (ν NH), 2225 (ν C=N), 1675 (ν C=O), 1620 (ν C=N). ^{1}H-NMR (DMSO-d_6: δ, ppm); 2.25 (s, 3H, Ar-CH_3), 2.35 (s, 3H, Ar-CH_3), 3.35 and 4.35 (2xt, J=7 Hz, 4H, CH_2CH_2), 5.95 (s, 1H, -CH-), 6.85-8.25 (m, 7H, Ar-H) and 11.6 (br, exchangeable with D_2O, 1H, -NH-).

*Reaction of compound **2** with amines and hydrazine. Formation of **7a-d**.*

A solution of compound **2** (0.01 mol) in 30 ml of absolute ethanol was refluxed with primary amines namely, benzylamine, aniline, *p*-toluidine, and/or hydrazine hydrate (0.01 mol) for 6 hr. After concentration and cooling, the product that separated was collected and recrystallised from the proper solvent to give **7a-d**. IR (KBr: ν, cm^{-1}); 3330-3170 (ν NH, broad), 1695-1690 (ν C=O), 1620-1615 (ν C=N). **7a** ^{1}H-NMR (DMSO-d_6: δ, ppm): 2.25 (s, 3H, Ar-H), 2.4 (s, 3H, Ar-H), 3.2 (d, 2H, -C-NH-$CH_2C_6H_5$), 4.6 (s, 2H, -CH_2-), 6.59-8.1 (m, 12H, Ar-H and cyclic -CH-) and 10.9 (br, 1H, exchangeable with D_2O, cyclic NH). **7d** ^{1}H-NMR ($CDCl_3$: δ, ppm): 2.25 (s, 3H, Ar-CH_3), 2.45 (s, 3H, Ar-CH_3), 4.95 (br, m, 3H, $NHNH_2$), 6.55-7.95 (m, 7H, Ar-H and cyclic CH) and 10.85 (br, exchangeable with D_2O, 1H, -NH).

*Reaction of compound **7d** with aromatic aldehydes. Formation of **8a-c**.*

A mixture of compound **7d** (0.01 mol) and aromatic aldehyde namely, benzaldehyde, anisaldehyde, and/or *p*-chlorobenzaldehyde (0.01 mol) in 30 ml of absolute ethanol was refluxed for 6 hr. After concentration and cooling the product that separated was triturated with light petrol (bp. 60-80°C) then recrystallised from the proper solvent to give **8a-c**. IR (KBr; ν, cm^{-1}); 3340-3240 (ν NH), 1695-1690 (ν C=O), 1620-1615 (ν C=N), **8a** ^{1}H-NMR (DMSO-d_6: δ, ppm); 2.25, 2.45 (2xs, 6H, 2xAr-CH_3), 3.95 (s, 1H, NH-N=CH-Ar), 5.85 (s, 1H, -CH-), 6.85-8.55 (m, 12H, Ar-H) and 10.75 (br, exchangeable with D_2O, 1H, -NH-).

*Reaction of compound **7d** with acetylacetone. Formation of **9**.*

A mixture of compound **7d** (0.01 mol) and acetylacetone (0.01 mol) in 30 ml of absolute ethanol was refluxed for 6 hr. After concentration and cooling, the product was triturated with light petrol (bp. 60-80°C), then recrystallised from ethanol to give **9**. IR (KBr; ν, cm^{-1}); 3320 (ν NH), 1690 (ν C=O), and 1620 (ν C=N). ^{1}H-NMR ($CDCl_3$; δ, ppm): 1.2, 1.35 (2xs, 6H, 2xCH_3), 2.25, 2.35 (2xs, 6H, 2xAr-CH_3), 6.05 (s, 1H, -CH-), 6.7-8.15 (m, 7H, Ar-H, and cyclic -CH), and 10.8 (br, 1H, cyclic -NH).

*Reaction of compound **7d** with ethyl chloroacetate. Formation of **10**.*

A mixture of compound **7d** (0.01 mol), and ethyl chloroacetate (0.01 mol) in 30 ml of absolute ethanol was refluxed for 6 hr. The product that separated after concentration and cooling was recrystallised from ethanol to give **10**. IR (KBr; ν; cm^{-1}); 3340-3220 (ν NH), 1690 (ν C=O), 1665 (ν C=O, amide), 1615 (ν C=N) and 660 (ν C-Cl). ^{1}H-NMR ($CDCl_3$; δ, ppm): 2.2, 2.35 (2xs, 6H, 2xAr-CH_3), 4.6 (s, 2H, -CH_2-), 5.4 (br, 2H, NH-NH), 6.9-8.2 (m, 7H, Ar-H), and 10.8 (br, exchangeable with D_2O, 1H, cyclic -NH-).

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