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SOME REACTIONS OF 6,8-DIBROMO-2-PROPENYL-4H-3,1-BENZOXAZIN-4-ONE WITH NITROGEN NUCLEOPHILES UNDER MICROWAVE IRRADIATION

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Abstract

The benzoxazinone derivative **(1)** was prepared upon the action of crotonoyl chloride on 3,5-dibromoanthranilic acid in pyridine. Microwave irradiation assisted the aminolysis of **(1)** with nitrogen nucleophiles as benzyl amine, hydrazine hydrate and formamide to give the amide derivatives **(2a-c)** respectively. Quinazolinone derivatives **(3a-e)** were produced upon the action of primary amines such as m-nitroaniline, p-toluidine, p-anisidine, benzyl amine and/or hydrazine hydrate respectively on the benzoxazinone derivative **(1)**. An excess amount of p-anisidine, phenylhydrazine and/or p-toluidine afforded the amide and quinazolinone derivatives **(4a & 5a)**, **(4b & 5b)** and/or **(5c)** respectively. The benzoxazinone derivative **(1)** was subjected to react with secondary amines as piperidine or morpholine giving the amide derivatives **(6a)** or **(6b)** respectively under 1 : 1 molar ratio, while under 1 : 2 molar ratio, the dipiperidiyl or dimorphonyl derivatives **(7a)** or **(7b)** were formed respectively. Ammonolysis of **(1)** using ammonium acetate, yielded the quinazolinone derivative **(8)**.

Introduction

The utility of microwaves in heterocyclic synthesis is now receiving considerable attention[1-4] and although reactions of different benzoxazinone derivatives with nitrogen nucleophiles have been extensively investigated[5,6], the solventless reactions of benzoxazinone with nitrogen nucleophiles under microwave irradiation have not, to our knowledge, been previously investigated. As a part of a recent project, aiming to explore potential utility of microwaves as an energy source for heterocyclic synthesis, we report here on synthesis of new quinazolinone and amide derivatives of expected biological activities as; anticonvalsant[7,8], antihistaminic[9], antihypertensive[10], fungicidal[5] and as antimicrobial[11].

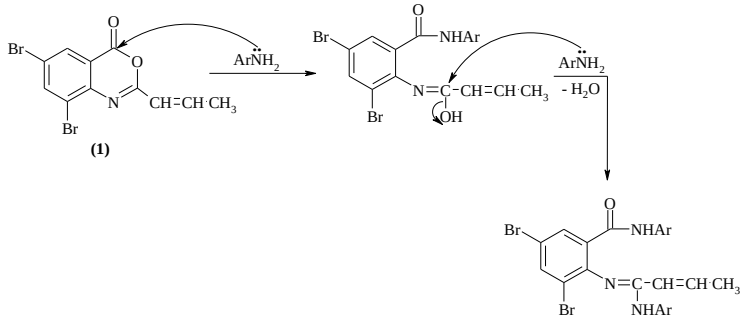
Results and discussion:

6,8-Dibromo-2-propenyl-4H-3,1-benzoxazine-4-one **(1)** was synthesized, when a solution of 3,5-dibromoanthranilic acid was stirred with equimolar ratio of crotonoyl chloride. Unlike other benzoxazinone derivatives[5,6], the opened acid amide derivative (which obtained upon elimination of HCl from dibromoanthranilic acid

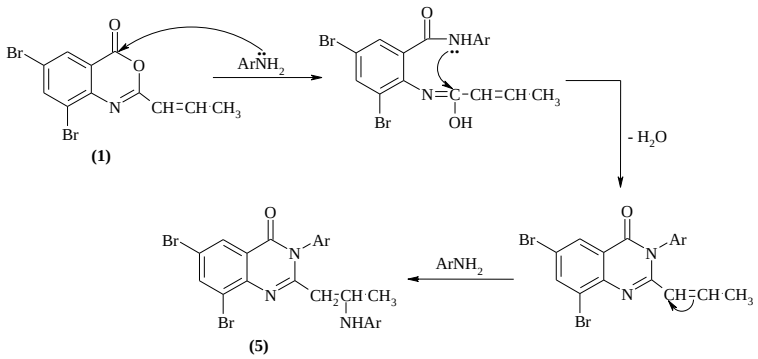
and acid chloride) was not isolated in our benzoxazinone under investigation, which revealed the high stability of the lactone form (benzoxazinone form). In contrast to Ismail[12] and El-Khamry[5,6], nucleophilic attack on the benzoxazinone derivative **(1)** depends not only on the type of the applied amines, but also, on the reaction conditions as well as, on the nature of benzoxazinone under investigation, where aminolysis or hydrazinolysis of the benzoxazinone derivative **(1)** with either benzylamine, hydrazine hydrate and/or formamide at 600 watt for 1 min., yielded 3,5-dibromo-2-crotonoylamino-N-benzylbenzamide **(2a)**, 3,5-dibromo-2-crotonoyl-amino benzoylhydrazine **(2b)** and/or 3,5-dibromo-2-crotonoylaminobenzoyl formamide **(2c)** respectively, while by increasing the power of the microwave to 900 watt and increasing the time of reaction to 5 min., the benzoxazinone derivative **(1)** underwent aminolysis by different manner, giving the quinazolinone derivatives **(3a-e)** upon action of m-nitroaniline, p-toluidine, p-anisidine, benzylamine and/or hydrazine hydrate respectively, where under these conditions, the microwave irradiation assisted the aminolysis of deactivated amines as m-nitroaniline, beside the subsequent cyclization.

On the other hand, reaction of **(1)** with an excess amount of p-anisidine gave a mixture of 3,5-dibromo-2-[butenylidene-4-anisidine-amino]-N-4-anisylbenzamide **(4a)** and 6,8-dibromo-2-[2-(4-anisyl)amino-propyl]-3-(4-anisyl)quinazolin-4-one **(5a)**, while hydrazinolysis of **(1)** using an excess amount of phenyl hydrazine yielded a mixture of 3,5-dibromo-2-[crotonaldehyde phenyl hydrazinamino]-N-phenylhydrazino benzamide **(4b)** and 6,8-dibromo-2-[2-phenylhydrazinylpropyl]-3-phenyl amino quinazolin-4-one **(5b)**.

Formation of **(4a)** and **(4b)** can be explained via the following mechanism :



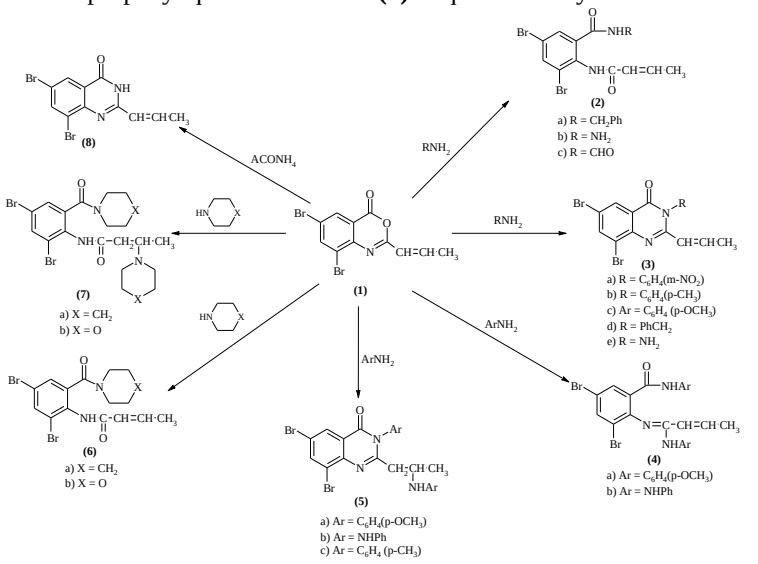
While formation of **(5a) (5b) (5c)** are explained via the following pathway:



a) Ar = $C_6H_4(p\text{-}OCH_3)$
b) Ar = NHPh
c) Ar = C_6H_4 (p-CH_3)

Unfortunately, aminolysis of **(1)** with an excess amount of p-toluidine yielded only, 6,8-dibromo-2-[2-(4-toluidine)propyl]-3-(4-tolyl) quinazolin-4-one **(5c)** as a sole product.

The benzoxazinone derivative **(1)** was allowed to react with secondary amines as piperidine and/or morpholine in 1:1 molar ratio, giving N-[3,5-dibromo-2-crotonoylaminobenzoyl]piperidine and/or morpholine **(6a)** and/or **(6b)** respectively, while in 1:2 molar ratio, two moles of secondary amines were added to give 2-[3-(piperidinyl) or (morpholinyl) butyroylamino]-3,5-dibromobenzoic piperidide or morpholide **(7a)** or **(7b)** respectively. It was found that, microwave irradiation of the benzoxazinone derivative **(1)** with ammonium acetate, afforded the expected, 6,8-dibromo-2-propenyl quinazolin-4-one **(8)** in quantitative yield.



a) Ar = $C_6H_4(p\text{-}OCH_3)$
b) Ar = NHPh
c) Ar = C_6H_4 (p-CH_3)

Table 1 : Characterization data of prepared compounds

Compd. No.	M.p°C (colour)	Yield % Solvent of recryst.	Mol Formula (M wt)	Analysis Calculated/found		
				C%	H%	N%
1	138-140 Pal yellow	45 Pb	$C_{11}H_7NO_2Br_2$ (345.00)	38.29 38.32	2.04 2.02	4.06 4.06
2a	230-232 White	60 M	$C_{18}H_{16}N_2O_2Br_2$ (452.15)	47.82 47.84	3.57 3.55	6.19 6.18
2b	168-170 Yellow	35 Pc	$C_{11}H_{11}N_3O_2Br_2$ (377.04)	35.04 35.10	2.94 2.93	11.14 11.14
2c	202-205 White	65 E	$C_{12}H_{10}N_2O_3Br_2$ (390.04)	36.95 36.99	2.58 2.60	7.18 7.17
3a	140-142 Yellow	60 B	$C_{17}H_{11}N_3O_3Br_2$ (465.11)	43.90 43.81	2.38 2.35	9.03 9.02
3b	216-217 White	60 E	$C_{18}H_{14}N_2OBr_2$ (434.14)	49.79 49.77	3.25 3.22	6.45 6.44
3c	170-173 Yellow	65 B	$C_{18}H_{14}N_2O_2Br_2$ (450.14)	48.03 48.01	3.13 3.13	6.22 6.22
3d	169-170 Yellow	80 B	$C_{18}H_{14}N_2OBr_2$ (434.14)	49.79 49.80	3.25 3.26	6.45 6.44
3e	146-149 Yellow	55 E	$C_{11}H_9N_3OBr_2$ (359.03)	36.79 36.80	2.53 2.55	11.70 11.72
4a	225-227 White	65 E	$C_{25}H_{23}N_3O_3Br_2$ (573.30)	52.37 52.40	4.04 4.02	7.33 7.31
4b	100-103 Red	70 Pb	$C_{23}H_{21}N_5OBr_2$ (543.29)	50.84 50.80	3.89 3.89	12.89 12.84
5a	145-147 Grey	70 E	$C_{25}H_{23}N_3O_3Br_2$ (573.30)	52.38 52.41	4.05 4.21	7.33 7.33
5b	73-75 Red	65 M	$C_{23}H_{21}N_5OBr_2$ (543.27)	50.85 50.90	3.89 3.88	12.89 12.90
5c	173-175 Yellow	60 E	$C_{25}H_{23}N_3OBr_2$ (541.30)	55.47 55.49	4.28 4.29	7.76 7.76
6a	115-119 White	40 M	$C_{16}H_{18}N_2O_2Br_2$ (430.15)	44.67 44.88	4.22 4.21	6.51 6.51
6b	183-186 White	65 B + M	$C_{15}H_{16}N_2O_3Br_2$ (432.12)	41.69 41.69	3.73 3.70	6.48 6.44
7a	163-165 White	75 Pb	$C_{21}H_{29}N_3O_2Br_2$ (515.30)	48.94 48.97	5.67 5.65	8.15 8.15
7b	160-162 White	70 B	$C_{19}H_{25}N_3O_4Br_2$ (519.25)	43.95 43.99	4.85 4.80	8.09 8.10
8	298-300 White	75 M	$C_{11}H_8N_2OBr_2$ (344.01)	38.40 38.38	2.34 2.33	8.14 8.14

Pa = petroleum 40-60, Pc = Petroleum 60-80, Pb = petroleum 80-100

B = benzene, M = methanol, E = ethanol

Table 2 : ^{1}H-NMR, MS and IR data of prepared compounds

Compd No.	^{1}H-NMR (δ in ppm)	MS (m/z, %)	IR cm^{-1}	
			ν_{N-H}	$\nu_{C=O}$
1	8.27 (d, 1H), 8.16 (d, 1H), 7.15 (m, 1H), 6.31 (d, 1H) and 2.05 (d, 3H)	$[M + 2]^+$ 347 (13%), 346 (5%), 345 (18%), 277 (6%), 69 (100%)	–	1758
2a	10.2 (broad, 2H), 7.82 (d, 1H), 7.60 (d, 1H), 7.33 (m, 5H), 6.98 (m, 1H), 6.1 (d, 1H), 4.51 (d, 2H) and 1.92 (d, 3H)	$[M + 3]^+$ 455 (1%), 454 (2%), 453 (2%), 435 (1%), 383 (10%), 69 (100%)	3266	1673 1645
2b	8.37 (d, 1H), 8.11 (d, 1H), 4.08 (m, 3H), 3.49 (s, 1H), 3.48 (m, 1H), 3.10 (d, 1H) and 1.47 (d, 3H)	$[M - 2]^+$ 375 (5%), 361 (15%), 344 (100%), 317 (11%), 288 (11%)	3251	1677 1653
2c	10.19 (s, 1H), 9.99 (s, 1H), 8.30 (d, 1H), 7.68 (d, 1H), 6.90 (m, 1H), 6.03 (d, 1H) and 1.93 (d, 3H).	$[M]^+$ 390 (6%), 389 (12%), 344 (71%), 162 (84%), 72 (100%)	3254	1682 1654
3a	8.45 (d, 1H), 8.35 (d, 1H), 8.33 (d, 1H), 8.22-7.5 (m, 3H), 7.48 (m, 1H), 5.66 (d, 1H) and 1.88 (d, 3H)	$[M +3]^+$ 468 (17%), 467 (22%), 466 (28%), 465 (43%), 420 (38%), 275 (40%), 153 (72%), 76 (100%)	–	1693
3b	8.08 (d, 1H), 7.75 (d, 1H), 7.56 (dd, 4H), 6.83 (m, 1H), 6.11 (d, 1H), 2.22 (s, 3H) and 1.82 (d, 3H)	$[M]^+$ 434 (3%), 433 (3%), 346 (12%), 107 (100%), 69 (42%)	–	1674
3c	8.33 (d, 1H), 8.12 (d, 1H), 7.12 (m, 1H), 7.08 (dd, 4H), 5.79 (d, 1H), 3.91 (s, 3H) and 1.84 (d, 3H)	$[M + 4]^+$ 454 (2%), 453 (21%), 452 (64%), 451 (50%), 450 (100%), 288 (13%), 241 (58%), 77 (68%)	–	1688
3d	8.29 (d, 1H), 7.93 (d, 1H), 7.56-7.12 (m, 5H), 5.50 (d, 1H), 5.11 (d, 1H), 4.30 (d, 1H), 3.98-3.67 (m, 1H) and 1.49 (d, 3H)	$[M+3]^+$ 437 (4%), 436 (7%), 435 (9%), 434 (19%), 107 (14%), 91 (100%), 77 (13.5%), 65 (31%)	–	1692
3e	8.30 (d, 1H), 8.06 (d, 1H), 7.15 (m, 1H), 6.31 (d, 1H), 4.08 (m, 2H) and 1.44 (d, 3H)	$[M + 2]^+$ 361 (16%), 359 (28%), 344 (100%) 263 (11%), 153 (7%), 88 (15%), 74 (20%)	3217	1679
4a	10.15 (s, 1H), 9.71 (s, 1H), 8.17 (d, 1H), 7.75 (d, 1H), 7.58 (d, 4H), 6.91 (dd, 4H), 6.74 (m, 1H), 6.39 (d, 1H), 3.84 (s, 3H), 3.75 (s, 3H) and 1.81 (d, 3H)	$[M + 2]^+$ 575 (3.5%), 573 (7%), 451 (6%), 346 (11%), 278 (2%), 123 (100%), 69 (41%)	3392 3261	1674
4b	8.7 (b, 2H), 8.65 (b, 2H), 8.25 (d, 1H), 8.18 (d, 1H), 7.61-7.20 (m, 10H), 6.85 (m, 1H), 6.30 (d, 1H) and 1.85 (d, 3H)	$[M]^+$ 543 (11%), 432 (41%), 326 (14%), 118 (17%), 77 (100%), 69 (17%)	3470 3358 3282	1682

Compd No.	^{1}H-NMR (δ in ppm)	MS (m/z, %)	IR cm^{-1}	
			ν_{N-H}	$\nu_{C=O}$
5a	3.5 (hump, 1H), 8.27 (d, 1H), 8.10 (d, 1H), 7.00-6.55 (m, 8H), 3.9 (s, 3H), 3.74 (s, 3H), 2.62 (m, 1H), 1.25 (d, 2H) and 1.22 (d, 3H)	$[M + 2]^+$ 575 (6%), 573 (21%), 450 (30%), 327 (11%), 150 (100%), 108 (40%), 92 (22%), 77 (27%)	3392	1676
5b	8.71 (b, 2H), 8.62 (b, 1H), 8.24 (d, 1H), 8.19 (d, 1H), 7.56-7.25 (m, 10H), 4.61 (m, 1H), 2.24 (d, 2H) and 1.18 (d, 3H)	$[M - 1]^+$ 542 (2%), 541 (3%), 433 (18%), 117 (10%), 104 (41%), 92 (33%), 76 (100%), 65 (25%)	3447	1685
5c	8.40 (d, 2H), 8.17 (d, 1H), 7.36 (dd, 4H), 6.83 (dd, 4H), 5.22 (m, 1H), 2.73 (d, 2H), 2.50 (s, 3H), 2.25 (s, 3H) and 1.16 (d, 3H)	$[M+ 2]^+$ 543 (3%), 541 (4%), 407 (10%), 134 (100%), 91 (24%)	3376	1681
6a	8.63 (s, 1H), 7.68 (d, 1H), 7.28 (d, 1H), 6.90 (m, 1H), 6.07 (d, 1H), 3.74-3.30 (m, 4H), 1.90 (d, 3H) and 1.62-1.48 (m, 6H)	$[M + 1]^+$ 431 (1%), 430 (3%), 278 (3%), 168 (3%), 84 (100%), 69 (65%)	3505 3454 3212 3184	1679 1644
6b	8.20 (s, 1H), 7.73 (d, 1H), 7.30 (d, 1H), 6.93 (m, 1H), 6.03 (d, 1H), 3.8 (m, 4H), 3.45 (m, 4H) and 1.93 (d, 3H)	$[M]^+$ 432 (2%), 431 (3%), 430 (2%), 346 (24%), 280 (5%), 170 (2.5%), 88 (8.5%), 69 (100%), 56 (19%)	3220 3187	1687 1649.5
7a	8.83 (s, 1H), 7.65 (d, 1H), 7.26 (d, 1H), 3.71-3.29 (m, 9H), 2.35 (d, 2H), 1.89 (d, 3H) and 1.43 (b, 12H)	$[M + 3]^+$ 518 (4%), 516 (12%), 515 (3%), 413 (26%), 172 (2%), 86 (100%)	3503 3451	1678 1644
7b	10.95 (s, 1H), 7.80 (d, 1H), 7.30 (d, 1H), 3.83-3.13 (m, 8H), 2.71-2.36 (m, 2H), 2.30 (m, 2H) and 1.11 (t, 3H)	$[M + 3]^+$ 522 (2%), 521 (3%), 519 (6%), 476 (10%), 114 (100%), 69 (11%), 56 (26%)	3215 3152	1670 1646
8	9.57 (s, 1H), 8.01 (d, 1H), 7.65 (d, 1H), 6.78 (m, 1H), 6.17 (d, 1H) and 1.86 (d, 3H)	$[M + 2]^+$ 346 (2%), 345 (2%), 344 (3%), 281 (11%), 69 (100%)	3407 3278	1672

Experimental

Melting points reported are uncorrected. IR spectra were recorded on Pye-Unicam SP1200 spectrophotometer using the KBr wafer technique. The ^{1}H-NMR were determined on a Varian Gemini 200 MHz Brucher Ac-200 MHz using TMS as internal standard (chemical shifts in δ-scale). The mass spectra were determined using HP model MS-5988 at electron energy 70 eV.

Synthesis of compounds

6,8-Dibromo-2-propenyl-4H-3,1-benzoxazin-4-one (1)

To a solution of 3,5-dibromoanthranlic acid (0.01 mol) in pyridine (50 mL), the crotonoyl chloride (0.01 mol) was added dropwise at room temperature with stirring for 2 hr. The reaction mixture was poured on ice cold hydrochloric acid, the produced mass was filtered washed with water and crystallized to give **(1)**.

3,5-Dibromo-2-crotonoylamino-N-benzylbenzamide (2a), 3,5-dibromo-2-crotonoylaminobenzoylhydrazine (2b) and 3,5-dibromo-2-crotonoyl-aminobenzoylformamide (2c)

A mixture of **(1)** (0.01 mol), benzylamine (0.02 mol), hydrazine hydrate (0.02 mol) and/or formamide (0.02 mol) was exposed to a microwave at 600 watt for 1 min. After cooling the reaction mixture was poured on ice cold hydrochloric acid, the solid mass formed crystallized to give **(2a-c)**.

6,8-Dibromo-2-propenyl-3-(3-nitrophenyl)quinazolin-4-one (3a), 6,8-dibromo-2-propenyl-3-(4-tolyl)quinazolin-4-one (3b), 6,8-dibromo-2-propenyl-3-(4-anisyl)quinazolin-4-one (3c), 6,8-dibromo-2-propenyl-3-benzylquinazolin-4-one (3d) and 6,8-dibromo-2-propenyl-3-amino-quinazolin-4-one (3e)

A mixture of **(1)** (0.01 mol) and m-nitroaniline, p-toluidine, p-anisidine, benzylamine and/or hydrazine hydrate (0.01 mol) was exposed to a microwave at 900 watt for 5 min. After cooling, the reaction mixture was treated with ice cold HCl. The solid mass formed was filtered and crystallized to give **(3a-e)** respectively.

3,5-Dibromo-2-(butenylidene-4-anisidineamino)-N-(4-anisyl) benz-amide (4a), 3,5-dibromo-2-(crotonaldehyde phenylhydrazine amino)-N-phenyl hydrazinobenzamide (4b), 6,8-dibromo-2-[2-(4-anisyl) aminopropyl]-3-(4-anisyl)quinazolin-4-one (5a) and 6,8-dibromo-2-[2-phenylhydrazinyl propyl]-3-phenylaminoquinazolin-4-one (5b)

A mixture of **(1)** (0.01 mol), p-anisidine, and/or phenylhydrazine (0.02 mol) was exposed to a microwave at 900 watt for 5 min, after cooling, the reaction mixture was poured on ice cold HCl, the product mass was filtered off and crystallized to give **(4a)** & **(5a)** and/or **(4b)** & **(5b)** respectively.

6,8-Dibromo-2-[2-(4-toluidine)propyl]-3-(4-tolyl)quinazolin-4-one (5c)

A mixture of **(1)** (0.01 mol) and p-toluidine (0.02 mol) was exposed to a microwave at 900 watt for 5 min., after cooling, the reaction mixture was poured on ice HCl, the product mass was filtered off and crystallized to give **(5c).**

N-[3,5-dibromo-2-crotonoylaminobenzoyl]piperidine (6a) and N-[3,5-dibromo-2-crotonoylaminobenzoyl]morpholine (6b)

A mixture of **(1)** (0.01 mol), piperidine and/or morpholine (0.01 mol) was exposed to microwave at 900 watt for 3 min after cooling the reaction mixture was poured on ice cold HCl, then the solid formed was filtered off and crystallized to give **(6a)** and/or **(6b)** respectively.

2-[3-(Piperidinyl)butyroylamino]-3,5-dibromobenzoic piperidine (7a) and 2-[3-(morpholinyl)butyroylamino]-3,5-dibromobenzoic mor-phoilde (7b).

A mixture of **(1)** (0.01 mol), piperidine and/or morphaline (0.02 mol) was exposed to microwave at 900 watt for 3 min, after cooling the reaction mixture was poured on ice cold HCl, then the solid formed was filtered off and crystallized to give **(7a)** and/or **(7b)** respectively.

6,8-Dibromo-2-propenylquinazolin-4-one (8)

A mixture of **(1)** (0.01 mol) and ammonium acetate (0.04 mol) was exposed to microwave at 600 watt for 1 min., after cooling, the reaction mixture was triturated with warm water and the solid formed was filtered off, and crystallized to give **(8)**.

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