MICROWAVE-ASSISTED REACTION 3[1]. ONE POT SYNTHESIS OF PYRIMIDO[1,2-a]-6,7,8,9-TETRAHYDROQUINAZOLINES AND PYRIMIDO[1,2-a]-2,3-DIHYDRO-5-AZAINDENES

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Abstract:
One pot synthesis of pyrimido[1,2-a]-6,7,8,9-tetrahydroquinazolines and pyrimido[1,2-a]-2,3-dihydro-5-azaindenes via reaction of 2-aminopyrimidine **1**, cyclic ketones **2** and aromatic aldehydes **3** under microwave irradiation has been reported.

Introduction

The importance of bicyclic guanidines is well recognised by synthetic as well as biological chemists (2,3). With the development of pyrimido[1,2-a]pyrimidines as useful oxoanion binding molecules in open-chain artificial receptors (4) and as hypoglycemic active compounds (5) there has been a marked interest in the synthesis of this ring system. On the other hand, several pharmaceuticals contain the quinazoline ring system, these include the sedative methaqualone and prazosine, are known as an antihypertensive agents. The organic synthesis under microwave heating techinque and without solvent is now receiving considerable interest (6,7). It is worth mentioning that this techinque offers many advantages. Solvents are usually toxic, expensive, difficult to remove particularly in the case of aprotic polar solvents with high boiling points and are environments air polluting agents.

Results and discussion

As a part of our program aiming to synthesis polyfuncionally substituted condensed heterocycles via simple routes and unexpensive starting materials (8,9), we report here a new one pot synthesis of pyrimido[1,2-a]-6,7,8,9-tetrahydroquinazolines and pyrimido[1,2-a]-2,3-dihydro-5-

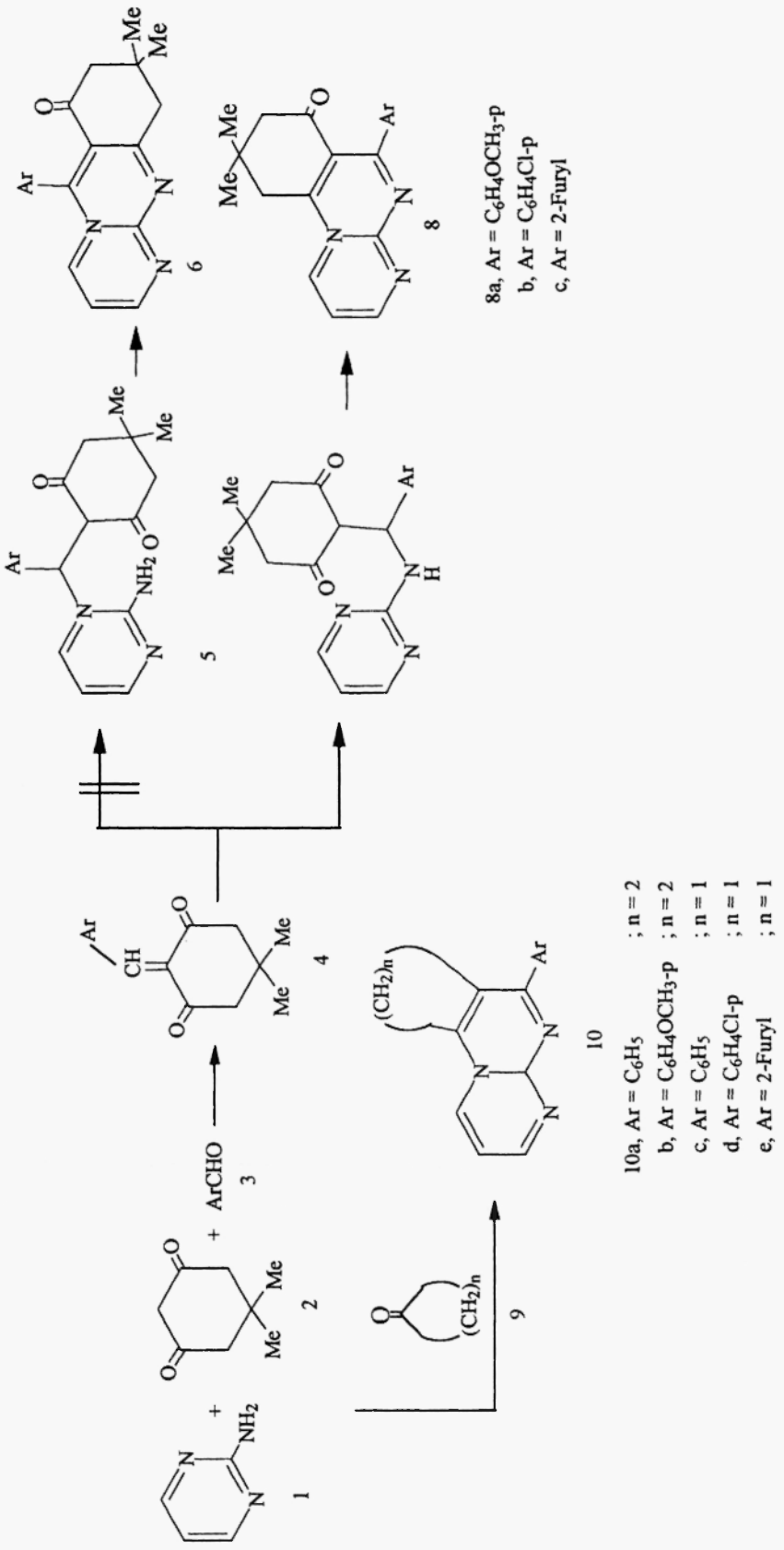
azaindenes by reaction of 2-aminopyrimidine **1**, cyclic ketones **2** and aromatic aldehydes **3** under microwave irradiation. Thus, when an equimolecular mixture of 2-aminopyrimidine **1**, dimedone **2** and 4-methoxybenzaldehyde **3a** - in presence of a catalytic amount of piperidine - was irradiated in a microwave oven for 30 minutes at 650 watts, a compound of molecular formula $[C_{20}H_{21}N_3O_2]$; $[M^+]$ = 335.5 was obtained in an excellent yield. The reaction gave a single product as determined on TLC. The IR spectrum of the reaction product showed the presence of both methyl and C=N functions at υ = 2290 and 1650 cm^{-1}. The ^1H NMR revealed two methyl groups at δ =1.01 and 1.21 ppm, a broad singlet at δ = 2.03 that integrated for two protons, a singlet for two protons at δ = 3.37 in addition to signal for $-OCH_3$ function at δ = 3.6 ppm and a multiplet for aromatic protons at δ = 6.72-8.28. Two isomeric structures seemed possible for the reaction product, the linear and angular forms **6** and **8**. Although the spectrum of the reaction product can be interpreted in terms of both structures **7**, **8**, structure **8** is established for the reaction product based on the fact that for 2-aminopyrimidine, the amino form exists in the amino rather than the dihydroimino tautomer (10). The formation of **8** was assumed to be formed via condensation of the aromatic aldehyde with the methylene group flanked by the two carbonyl groups to afford the ylidenic product **4** followed by addition of the less hindered exocyclic amino function to the activated double bond in **4** to form the Michael adduct **7** which was then cyclised and aromatised to form the final isolable product **8**. Addition of the ring nitrogen to the activated double bond in **4** will afford **5** which in cyclisation will afford the linear isomer **7**. Similarly, the reaction of **1, 2** and **3b-d** under the same reaction conditions afforded **8b-d**.

In order to extend this reaction to other cyclic ketones, compound **1** was allowed to react with **3** and **9a-e**. Compounds **10a-e** were obtained via a similar reaction mechanism and their structure was established based on analytical and spectral data.

The results obtained presents a simple, environmental clean and high yield process for the synthesis of an interesting fused heterocycles with expected biological activity.

Experimental

All melting points are uncorrected. IR spectra were recorded in KBr with Shimadzu 470 spectrophotometer. ^1H NMR were recorded on a Varian EM-390 400 MHz spectrometer in $[^2H_6]$ DMSO as solvent and TMS as internal standard, chemical shifts are reported in δ units (ppm). Mass


1
2
ArCHO
3
4
5
6
8
9
10
8a, Ar = C6H4OCH3-p
b, Ar = C6H4Cl-p
c, Ar = 2-Furyl
10a, Ar = C6H5 ; n = 2
b, Ar = C6H4OCH3-p ; n = 2
c, Ar = C6H5 ; n = 1
d, Ar = C6H4Cl-p ; n = 1
e, Ar = 2-Furyl ; n = 1

spectra were measured on Joel JMS 600 at 70 ev. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University.

General procedure for the reaction of 2-aminopyrimidine 1, cyclic ketone 2 and aromatic aldehydes 3:

To a mixture of 2-aminopyrimidine **1** (0.951 g, 0.01m mol), (0.01 m mol) cyclic ketone **2, 9** and (0.01 m mol) aromatic aldehyde **3a-e** in the presence of catalytic amount of piperidine was irradiated in microwave oven for 3 minutes at 650 watts. After cooling to room temperature, the solid product formed was collected by filtration, dried and recrystallized from ethanol.

7,7-Dimethyl-10-(4-methoxyphenyl)-9-oxopyrimido[1,2-a]-6,7,8,9-tetrahydroquinazoline 8a:

Yield: 2.85 g (85%); M.P. 120 °C. IR (KBr) υ_{max} = 2290 (CH_3), 1650 cm^{-1} (C=N). - MS (EI, 70 EV): m/z (%) = 335.5 [M^+]. - ^1H NMR (DMSO) δ_H = 1.01 (s, 3H, CH_3), 1.21 (s, 3H,CH_3), 2.03 (br, s, 2H, $CH_{2\text{-}6}$), 3.37 (s, 2H, $CH_{2\text{-}8}$), 3.6 (s, 3H, OCH_3), 6.72-8.28 (m, 8H, arom-H). - $C_{20}H_{21}N_3O_2$ (335.40): Calcd. C 71.62, H 6.31, N 12.52; Found. C 71.63, H 6.22, N 12.55.

7,7-Dimethyl-10-(4-chlorophenyl)-9-oxopyrimido[1,2-a]-6,7,8,9-tetrahydroquinazoline 8b:

Yield: 2.78 g (82%); M.P. 115°C. IR (KBr) υ_{max} = 2290 (CH_3), 1660 cm^{-1} (C=N). - MS (EI, 70 EV): m/z (%) = 339.9 [M^+]. - ^1H NMR (DMSO) δ_H = 1.01 (s, 3H, CH_3), 1.21 (s, 3H,CH_3), 2.04 (s, 2H, $CH_{2\text{-}6}$), 3.34 (s, 2H, $CH_{2\text{-}8}$), 6.84-8.03 (m, 8H, arom-H). - $C_{19}H_{18}N_3OCl$ (339.82): Calcd. C 67.15, H 5.33, N 12.36, CI 10.43; Found. C 67.22, H 5.42, N 12.52, CI 10.45.

7,7-Dimethyl-10-(3-nitrophenyl)-9-oxopyrimido[1,2-a]-6,7,8,9-tetrahydroquinazoline 8c :

Yield: 2.94 g (84%); M.P. 170°C. IR (KBr) υ_{max} = 2290 (CH_3), 1580 cm^{-1} (C=N). - ^1H NMR (DMSO) δ_H = 1.03 (s, 3H, CH_3), 1.11 (s, 3H,CH_3), 1.96 (s, 2H, $CH_{2\text{-}6}$), 3.33 (s, 2H, $CH_{2\text{-}8}$), 6.19-8.0 (m, 8H, arom-H). - $C_{19}H_{18}N_4O_3$ (350.38): Calcd. C 65.13, H 5.17, N 15.99; Found. C 65.22, H 5.18, N 16.0.

7,7-Dimethyl-10-(2-furyl)-9-oxopyrimido[1,2-a]-6,7,8,9-tetrahydroquinazoline 8d :

Yield: 2.45 g (83%); M.P. 170°C. IR (KBr) υ_{max} = 2295 (CH_3), 1650 cm^{-1} (C=N). - MS (EI, 70 EV): m/z (%) = 295.0 [M^+]. Insoluble in commonly used ^1H NMR solvents. - $C_{17}H_{17}N_3O_2$ (295.34): Calcd. C 69.13, H 5.80, N 14.22; Found. C 69.22, H 5.82, N 14.25.

10-Phenylpyrimido[1,2-a]-6,7,8,9-tetrahydroquinazoline 10a :

Yield: 2.15 g (82%); M.P. 260°C. IR (KBr) υ_{max} = 1650 cm^{-1} (C=N). - MS (EI, 70 EV): m/z (%) = 263.9 [M^+]. Insoluble in commonly used ^1H NMR solvents. - $C_{17}H_{17}N_3$ (263.34): Calcd. C 77.53, H 6.50, N 15.95; Found. C 77.55, H 6.62, N 15.88.

10-(4-Methoxyphenyl)-pyrimido[1,2-a]-6,7,8,9-tetrahydroquinazoline 10b :

Yield: 2.49 g (85%); M.P. 160°C. IR (KBr) υ_{max} = 1650 cm^{-1} (C=N). - MS (EI, 70 EV): m/z (%) = 292.3 [M^+]. ^1H NMR (DMSO) δ_H = 1.7-1.86 (m, 9H, $4CH_2$ groups), 3.78 (s, 3H,OCH_3), 6.6-7.57 (m, 8H, arom-H). - $C_{18}H_{19}N_3O$ (293.37): Calcd. C 73.69, H 6.52, N 14.32; Found. C 73.77, H 6.49, N 14.35.

4-Phenylpyrimido[1,2-a]-2,3-dihydro-5-azaindene 10c :

Yield: 2.06 g (83%); M.P. 150°C. IR (KBr) υ_{max} = 2290 cm^{-1} (CH- stretching), 1650 cm^{-1} (C=N). - MS (EI, 70 EV): m/z (%) = 249.1 [M^+]. ^1H NMR (DMSO) δ_H = 2.48-2.6 (m, 6H, $3CH_2$ groups), 3.38 (s, 3H,OCH_3), 7.12-7.69 (m, 9H, arom-H). - $C_{16}H_{15}N_3$ (249.31): Calcd. C 77.08, H 6.06, N 16.85; Found. C 77.22, H 6.21, N 16.88.

4-(4-Chlorophenyl)-pyrimido[1,2-a]-2,3-dihydro-5-azaindene 10d :

Yield: 2.29 g (81%); M.P. 225°C. IR (KBr) υ_{max} = 2290 cm^{-1} (CH- stretching), 1650 cm^{-1} (C=N). - MS (EI, 70 EV): m/z (%) = 283.5 [M^+]. Insoluble in commonly used ^1H NMR solvents. - $C_{16}H_{14}N_3Cl$ (283.76): Calcd. C 67.72, H 4.97, N 14.80, Cl 12.50; Found. C 67.77, H 5.02, N 14.85, Cl 12.52.

4-(2-Furyl)-pyrimido[1,2-a]-2,3-dihydro-5-azaindene 10e :

Yield: 1.96 g (83%); M.P. 235°C. IR (KBr) υ_{max} = 2290 cm^{-1} (CH- stretching), 1580 cm^{-1} (C=N). - MS (EI, 70 EV): m/z (%) = 239.6 [M^+]. ^1H NMR (DMSO) δ_H = 2.20-2.28 (m, 6H, $3CH_2$ protons), 6.29-8.8 (m, 7H,furyl and arom-H). - $C_{14}H_{13}N_3O$ (239.27): Calcd. C 70.27, H 5.47, N 17.56; Found. C 70.33, H 5.52, N 17.44.

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