Microwave Induced New Route to Acridine and Quinazoline Derivatives Using TLC Plates

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Microwave (MW) assisted synthesis of acridine and quinazoline derivatives was performed on thin layer chromatography (TLC) plates. This versatile, simple and economical green methodology is readily amenable to parallel synthesis of acridine and quinazoline compound libraries.

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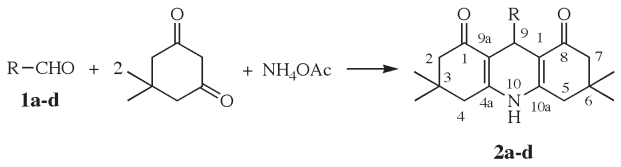
In designing ecofriendly synthesis [1] of the target molecule the starting materials are made to react by modifying the reaction conditions in such a way that it not only eliminates byproducts and wastes but also minimizes the use of organic solvents [2]. Over the past decade Hantzsch [3] and Biginelli [4] reactions have received considerable attention as a consequence of the pharmacological profile of 1,4-dihydropyridines (1,4-DHP) and 3,4-dihydropyrimidines as calcium channel blockers [5]. These classes of compounds have been synthesized in our laboratory [6] with modified procedures [7]. Thin layer chromatography has been reported as a tool for reaction optimization in microwave assisted synthesis [8]. This prompted us to modify this procedure for an efficient synthesis of 9-substituted-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (**2a-d**) and 4-substituted-7,7-dimethyl-2-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (**3a-d**) *via* cyclocondensation reaction of aldehyde (**1a-d**), dimedone, ammonium acetate/thiourea by simply spotting of the above reaction mixture on TLC plate and then subjecting it to microwave irradiation.

In a typical experiment, a test reaction was carried out on a 5 x 20 cm TLC plate. A spot of solution of benzaldehyde (0.1 mol, 0.101 mL), dimedone (0.2 mol, 0.280 g), ammonium acetate (0.1 mol, 0.077 g) in 2 mL methanol for Hantzsch reaction and a spot of solution of benzaldehyde (0.1 mol, 0.101 mL), dimedone (0.1 mol, 0.140 g) and thiourea (0.1 mol, 0.076 g) in 2 mL methanol for Biginelli reaction was placed on a TLC plate and was subjected to MWI at low power (560 Watts) at an interval of 40 seconds intermittently. Then the TLC plate was run in an appropriate system (Table 1). To our surprise, a prominent spot of product was seen, the rf value of which was consistent with that of the expected product (prepared by solid supported MW method for comparison) although some amount of unreacted reactants were also observed. In order to get an appreciable yield of pure products the reaction was carried out on a preparative TLC plate. An array of spots of 1:2:1 mole ratio of reactants for the synthesis of acridine and 1:1:1 mole ratio of reactants for the synthesis of quinazolines in 1 ml methanol was put on a preparative TLC plate along with a reference TLC with two spots one of the reactants and other of the expected product (Figure 1a and Figure 1b). Both the plates were subjected to MWI intermittently at an interval of 40s at low power. The reference TLC was viewed in an iodine chamber and accordingly that portion of silica gel containing the product was scratched from the preparative TLC plate and the product was extracted in $CHCl_3$. Evaporation of the solvent afforded the desired product, which was recrystallized from ethanol. Use of different heterocyclic aldehydes led to the synthesis of some novel acridine and quinazoline derivatives. The structure of the products was confirmed on the basis of spectroscopic data. The appearance of singlet at δ 5.5 due to H-9 and δ 4.6 due to H-4 in ^{1}H NMR and signals at δ 32.5 due to C-9 and δ 51.2 due to C-4 in ^{13}C NMR for compounds **2a-d** and **3a-d** respectively confirmed the formation of product. In IR the appearance of broad band at 3440 cm^{-1} due to NH and band at 1660 due to C=C further confirmed the formation of products.

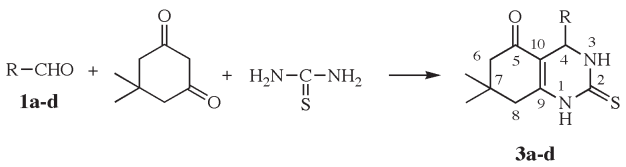
In conclusion, we have shown the viability and uniqueness of this method that can serve as a useful tool for rapid reaction optimization, which is necessary prior to library synthesis. The advantages of this ecologically safe protocol includes a simple reaction set up that does not require specialized equipment, shorter reaction time, elimination of solvent, cleaner products, optimum use of

Scheme 1



Synthesis of acridine derivatives

Scheme 2



Synthesis of quinazoline derivatives

Table 1

TLC System and Reaction Time for Compounds **2a-d** and **3a-d** [a]

Compound No.	R	m.p. (°C)	TLC system Benzene:EthylAcetate	Time (min.)	Yield (%)
2a	Phenyl	190-192 [10]	80:20	4.3	82
2b	4-Chlorophenyl	296-298 [11]	80:20	3.2	84
2c	Piperonyl	324-325 [11]	90:10	4.0	83
2d	2-Chloro-3-quinolyl	>300	60:40	3.2	80
3a	Phenyl	160-162 [12]	80:20	2.0	85
3b	4-Chlorophenyl	218-220	90:10	3.2	83
3c	Piperonyl	208-210	80:20	2.3	86
3d	2-Chloro-3-quinolyl	298-300	60:40	3.2	81

[a] Microwave Heating (560 W, 2450 MHz, 95-105 °C, 40 seconds).

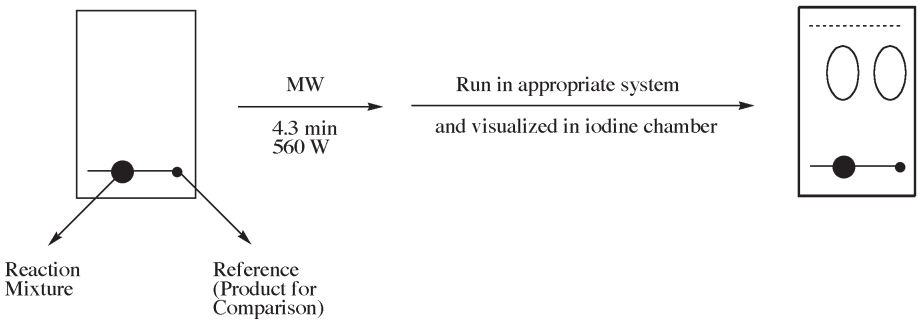


Figure 1a Schematic of reference thin layer chromatography for acridine derivatives

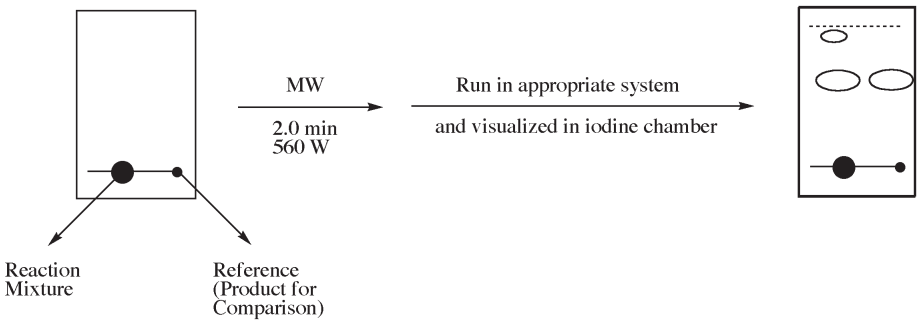


Figure 1b Schematic of reference thin layer chromatography for quinazoline derivatives

energy and usage of only few milligram of reactants in a few drops of solvent.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT IR-1710 spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance Spectrospin 300 (300 MHz) instrument using TMS as internal standard and $CDCl_3$ as solvent. Elemental analysis was performed on a Heraeus CHN Rapid Analyser. Microwave irradiation was carried out in Kenstar Microwave Oven, Model No. OM 9925E (2450 MHz, 800 W). Temperature of the reaction was measured through AZ, Mini Gun Type, Non-Contact IR Thermometer, Model No. 8868. Reactions were carried and monitored by thin layer chromatography plates (5 x 20 cm) with 0.2 mm silica Gel (G Spectrochem. Cat. No. 011904) and the spots were viewed in UV or iodine chamber. Dimedone, aldehydes (benzaldehyde, 4-chlorobenzaldehyde, piperonal), thiourea and ammonium acetate were obtained from commercial sources. 2-Chloro-3-quinoline aldehyde was prepared by literature method [9].

3,3,6,6-Tetramethyl-9-phenyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (**2a**).

This compound has the following spectral properties: ir: NH 3436, C=C 1660 cm^{-1}; ^1H nmr: δ 1.09 (s, 6H, $2CH_3$), 1.23 (s, 6H, $2CH_3$), 2.28-2.38 (m, 8H, CH_2), 5.55 (s, 1H, H-9), 7.08-7.22 (m, 5H, Ar-H), 11.88 (s, 1H, NH). ^{13}C nmr: δ 190.8 (C1, C8), 150.5 (C4a, C10a), 138.0, 128.2, 126.7, 125.8 (phenyl), 115.8 (C8a, C9a), 47.0 (C2, C7), 46.8 (C4, C5), 33.1 (C9), 31.6 (C3, C6), 29.6, 27.5 ($4CH_3$).

Anal. Calcd. for $C_{23}H_{27}NO_2$: C, 79.08; H, 7.73; N, 4.01. Found: C, 79.28; H, 7.68; N, 4.18.

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (**2b**).

This compound has the following spectral properties: ir: NH 3340, C=C 1665 cm^{-1}. ^1H nmr: δ 0.96 (s, 6H, $2CH_3$), 1.08 (s, 6H, $2CH_3$), 2.21-2.26 (m, 8H, CH_2), 5.45 (s, 1H, H-9), 7.12-7.33 (m, 4H, Ar-H), 11.90 (s, 1H, NH). ^{13}C nmr: δ 196.1 (C1, C8), 148.8 (C4a, C10a), 139.2, 131.0, 129.7, 128.7 (aryl), 114.5 (C8a, C9a), 49.8 (C2, C7), 41.5 (C4, C5), 32.9 (C9), 32.6 (C3, C6), 29.4, 27.9 ($4CH_3$).

Anal. Calcd. for $C_{23}H_{26}ClNO_2$: C, 71.96; H, 6.77; N, 3.65. Found: C, 72.05; H, 6.85; N, 3.56.

3,3,6,6-Tetramethyl-9-piperonyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (**2c**).

This compound has the following spectral properties: ir: NH 3394, C=C 1635 cm^{-1}. ^1H nmr: δ 1.08 (s, 6H, $2CH_3$), 1.51 (s, 6H, $2CH_3$), 2.14-2.39 (m, 8H, CH_2), 5.12 (s, 1H, H-9), 5.83 (s, 2H, OCH_2), 6.61-6.92 (m, 3H, Ar-H), 11.72 (s, 1H, NH). ^{13}C nmr: δ 191.5 (C1, C8), 150.2 (C4a, C10a), 147.4, 144.8, 137.3, 121.6, 114.9, 91.3 (piperonyl), 115.1 (C8a, C9a), 46.8 (C2, C7), 46.2 (C4, C5), 32.7 (C9), 31.1 (C3, C6), 29.5, 27.3 ($4CH_3$).

Anal. Calcd. for $C_{24}H_{27}NO_4$: C, 73.28; H, 6.87; N. 3.56. Found: C, 73.19; H, 6.68; N, 3.46.

3,3,6,6-Tetramethyl-9-(2-chloro-3-quinolyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (**2d**).

This compound has the following spectral properties: ir: NH 3380, C=C 1640 cm^{-1}. ^1H nmr: δ 0.97 (s, 6H, $2CH_3$), 1.13 (s, 6H, $2CH_3$), 2.21-2.35 (m, 8H, CH_2), 5.61 (s, 1H, H-9), 7.21-7.90 (m, 5H, quinolyl), 11.87 (s, 1H, NH). ^{13}C nmr: δ_ 193.7 (C1, C8), 151.1 (C4a, C10a), 166.8, 149.00, 136.8, 135.6, 130.8, 129.7, 128.7, 128.3, 126.8 (quinolyl), 115.7 (C8a, C9a), 48.9 (C2, C7), 42.3 (C4, C5), 31.8 (C9), 31.2 (C3, C6), 29.5, 27.6 ($4CH_3$).

Anal. Calcd. for $C_{26}H_{27}ClNO_2$: C, 74.19; H, 6.42; N, 3.32. Found: C, 74.25; H, 6.70; N, 3.04.

4-Phenyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (**3a**).

This compound has the following spectral properties: ir: NH 3443, C=C 1662 cm^{-1}. ^1H nmr: δ 0.97 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.18-2.45 (m, 4H, CH_2), 4.75 (s, 1H, H-4), 7.02-7.27 (m, 5H, Ar-H), 7.90 (s, 1H, NH), 10.81 (s, 1H, NH). ^{13}C nmr: δ 196.8 (C5), 162.7 (C2), 144.6 (C9), 128.9, 128.5, 128.4, 126.8 (phenyl), 116.2 (C10), 51.3 (C4), 41.7 (C6), 41.3 (C8), 32.7 (C7), 29.9, 27.8 ($2CH_3$).

Anal. Calcd. for $C_{16}H_{18}N_2OS$: C, 67.13; H, 6.29; N, 9.79. Found: C, 67.26; H, 6.38; N, 9.72.

4-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (**3b**).

This compound has the following spectral properties: ir: NH 3440, C=C 1635 cm^{-1}. ^1H nmr: δ 0.98 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.12-2.38 (m, 4H, CH_2), 4.72 (s, 1H, H-4), 7.14-7.43 (m, 4H, Ar-H), 7.82 (s, 1H, NH), 10.63 (s, 1H, NH). ^{13}C nmr: δ 196.1 (C5), 161.5 (C2), 143.8 (C9), 131.2, 129.4, 128.2, 126.2 (aryl), 115.7 (C10), 50.8 (C4), 41.4 (C6), 41.1 (C8), 32.3 (C7), 29.7, 27.7 ($2CH_3$).

Anal. Calcd. for $C_{16}H_{17}ClN_2OS$: C, 59.90; H, 5.30, N, 8.73. Found: C, 60.02; H, 5.56; N, 8.86.

4-Piperonyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (**3c**).

This compound has the following spectral properties: ir: NH 3430, C=C 1655 cm^{-1}. ^1H nmr: δ 0.97 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.15-2.48 (m, 4H, CH_2), 4.63 (s, 1H, H-4), 5.93 (s, 2H, OCH_2), 6.66-6.78 (m, 3H, Ar-H), 8.01 (s, 1H, NH), 10.52 (s, 1H, NH). ^{13}C nmr: δ 195.6 (C5), 161.2 (C2), 142.4 (C9), 147.4, 144.2, 128.5, 122.6, 114.2, 91.2 (piperonyl), 116.1 (C10), 51.0 (C4), 41.9 (C6), 41.3 (C8), 32.3 (C7), 29.2, 27.2 ($2CH_3$).

Anal. Calcd. for $C_{17}H_{18}N_2O_3S$: C, 61.81; H, 5.45; N, 8.48. Found: C, 61.70; H, 5.49; N, 8.52.

4-(2-Chloro-3-quinolyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (**3d**).

This compound has the following spectral properties: ir: NH 3431, C=C 1650 cm^{-1}. ^1H nmr: δ 1.00 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 2.18-2.42 (m, 4H, CH_2), 5.05 (s, 1H, H-4), 7.14-7.63 (m, 5H, quinolyl), 8.11 (s, 1H, NH), 11.31 (s, 1H, NH). ^{13}C nmr: δ 194.3 (C5), 160.8 (C2), 141.8 (C9), 166.5, 149.10, 135.3, 132.4, 130.5, 129.2, 128.5, 128.1, 126.2 (quinolyl), 115.8 (C10), 51.2 (C4), 41.5 (C6), 41.1 (C8), 31.7 (C7), 29.3, 27.7 ($2CH_3$).

Anal. Calcd. for $C_{19}H_{18}ClN_3OS$: C, 61.37; H, 4.84; N, 11.30. Found: C, 61.28; H, 4.96; N, 11.14.

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REFERENCES AND NOTES

[1] M. Kidwai, *Pure Appl. Chem.*, **73**, 1261 (2001).

[2a] M. Kidwai, S. Saxena, R. Mohan and R. Venkataramanan, *J. Chem. Soc.; Perkin Trans. 1*, **16**, 1845 (2002); [b] M. Kidwai, R. Venkataramanan and B. Dave, *J. Heterocyclic Chem.*, **39**, 1045 (2002).

[3a] A. Hantzsch, *Justus Liebigs Ann. Chem.*, **1**, 215 (1882); [b] R. Alajarin, J. J. Vaquero, J. L. G. Navio and J. Alvarez-Builla, *Synlett.*, 297 (1992).

[4a] P. Biginelli, *Gazz. Chim. Ital.*, **23**, 360 (1893); [b] C. O. Kappe, *Tetrahedron*, **49**, 6937 (1993); [c] D. S. Bose, L. Fatima and H. B. Mereyala, *J. Org. Chem.*, **68**, 587 (2003).

[5a] J. P. McCarthy, R. Zhang and S. Moreland, *J. Med. Chem.*, **38**, 119 (1995); [b] R. Fossheim, K. Svarteng, A. Mostad, C. Romming, E. Shefter and D. J. Triggle, *J. Med. Chem.*, **25**, 126 (1982).

[6] M. Kidwai and R. Mohan, *Canadian J. Chem.*, **82**, 427 (2004).

[7] M. Kidwai, R. Mohan and S. Saxena, *Russ. Chem. Bull.*, **52**, 2457 (2003).

[8] L. Williams, *Chem. Commun.*, 435 (2000).

[9] O. Meth Cohn, B. Narine and B. Tarnowski, *J. Chem. Soc. Perkin Trans. 1*, 1520 (1981).

[10] N. Martin, M. Quinteiro and C. Sewane, *J. Heterocyclic Chem.*, **32**, 235 (1995).

[11] S. J. Tu, Z. Lu, D. Shi, C. Yao, Y. Gao and C. Guo, *Synth. Commun.*, **32(14)**, 2181 (2002).

[12] M. Yarim, S. Sarac, M. Ertan, F. S. Kihc and K. Erol, *Arzneimittel-Forschung*, **52(1)**, 27 (2002).