Synthesis of Acridines by an Eco-friendly Method

GEORGE BRATULESCU*,
University of Craiova, Faculty of Mathematic and Natural Sciences, Department of Chemistry, 13 A.I.Cuza, 200585, Craiova, Romania

Acridine derivatives were synthesized via *a green methodology consisting in condensation reaction between diphenylamine and aliphatic or aromatic carboxylic acids in a heterogeneous medium. Good yields were obtained if the reaction medium contains a Lewis acid catalyst as zinc chloride and 2,2-dimethoxypropane as water scavenger. The products are easily separated from reaction medium and energy consumption is significantly reduced.*

Keywords: acridine, heterogeneous medium, green synthesis, Lewis acid, condensation reaction

The acridine nucleus is present in many natural organic compounds. The acridine derivatives have many pharmaceutical applications. Certain compounds are used as antitumor drugs [1-4]. Some acridine derivatives exhibit Anti-West Nile Virus activity [5]. Several acridine derivatives show anti-inflammatory, analgesic and kinase inhibition activities [6,7]. Certain acridines are used as anti-herpes [8] and DNA-binding agents [9]. The presence of the heteroatom of nitrogen in the ten position of the aromatic ring *skeleton* of acridines, involves intense *fluorescence spectra of the molecules* and the compounds are used as photosensitive organic dyes [10,11].

Conventional synthesis of acridine uses experimental protocols assigned to Friedlander, Bernthsen, Goldberg, Pfitzinger, or Ullman [12, 13]. These methods employ aromatic amines and carboxylic acid, strong Lewis or Brönsted acid catalysts, high temperature and long reaction time [12]. The acridines are obtained in low yields and many manipulations are required to isolate and purify the product of synthesis [14]. On the other hand, different proceedings of synthesis of acridine have been implemented and involve costly rare metallic catalysts, and many step reactions [15].

Lately, unconventional acridine syntheses with the help of microwaves [16-18] and ultrasonic irradiation [19] were developed. Some recent methodologies use as catalysts p-toluenesulphonic acid, ceric ammonium nitrate, zirconium oxychloride octahydrate, anhydrous aluminium chloride, and potassium dichromate. The large quantity of inorganic wastes generated, and the huge amount of toxic solvents employed to remove the products from reaction medium, limit the benefits of the methods [16]. Moreover, the yield of syntheses rarely reaches quasi-quantitative values [17].

The most employed methodology of obtaining acridines remains Bernthsen reaction. This method uses mixtures of carboxylic acids and aromatic amines. The reaction mixture is heated at high temperature (above 200°C) for a very log time (48 h). The Bernthsen reaction requires catalysts as anhydrous zinc chloride or polyphosphoric acid, but the yield reaches only 18-20% [20, 21].

Previously, we obtained acridine derivatives by Bernthsen method [18,22]. In this line we synthesized several substituted acridines using carboxylic aliphatic and aromatic acids, diphenylamine, 2,2-dimethoxypropane (DMP) like water scavenger and microwaves.

Experimental part

Reagents, equipment and methods

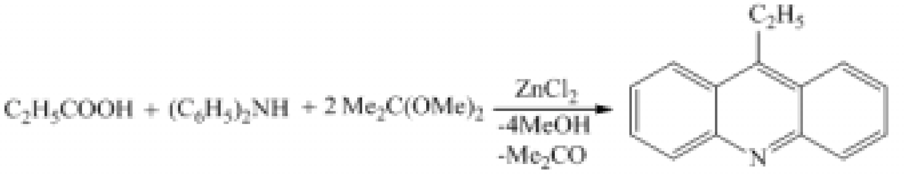
Diphenylamine, carboxylic acids, 2,2-dimethoxypropane, zinc chloride are commercially available substances. The obtained products were identified by TLC (silica gel, EtOH), elemental analysis and IR spectra. The IR/FT spectra were recorded using an ALPHA FTIR/ATR spectrometer fabricated by Bruker Optics GmbH. Elemental analyses were carried out with a Carlo Erba model 1106 elemental analyzer produced by Carlo Erba. The melting points were determined on a Gallenkamp digital melting point apparatus. A commercial microwave oven was employed.

General procedure of synthesis

In a Pyrex beaker were introduced diphenylamine (0.01 mol), 2,2-dimethoxypropane (0.02 mol), carboxylic acid (0.01 mol), and $ZnCl_2$ (0.02 mol). The mixture was well mixed. The medium reaction was irradiated in the microwave reactor (400 W) for the required time. The resulting residue was recrystallized from EtOH-$PhCH_3$ to give the acridine derivatives (table 2). Melting points of the acridine derivatives are identical with the literature melting points of the same compounds.

Results and discussions

To find optimal conditions of synthesis, we studied the reaction of obtaining 9-ethylacridine (table 1). The reaction *takes place* as follows:

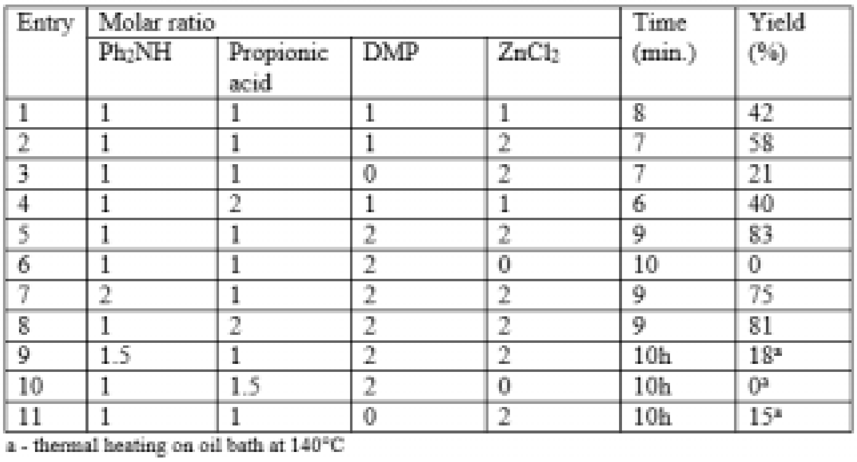


Reaction of condensation between *propionic acid and* diphenylamine doesn't occur if the reaction medium has not the catalyst $ZnCl_2$ (entry 6 and 10, table 1). A better yield is obtained if the reaction medium contains both $ZnCl_2$ and 2,2-dimethoxypropane. The optimal conditions for synthesis of 9-ethylacridine (entry 5, table 1) correspond to a molar ratio

---

* email: georgebratulescu@yahoo.com

Table 1
INFLUENCE OF SOME REACTION CONDITIONS ON THE OBTAINING OF 9-ETHYLACRIDINE



Entry	Molar ratio				Time (min.)	Yield (%)
	Ph_2NH	Propionic acid	DMP	$ZnCl_2$		
1	1	1	1	1	8	42
2	1	1	1	2	7	58
3	1	1	0	2	7	21
4	1	2	1	1	6	40
5	1	1	2	2	9	83
6	1	1	2	0	10	0
7	2	1	2	2	9	75
8	1	2	2	2	9	81
9	1.5	1	2	2	10h	18^a
10	1	1.5	2	0	10h	0^a
11	1	1	0	2	10h	15^a

a - thermal heating on oil bath at 140°C

between reagents, diphenyl amine: propionic acid: DMP: $ZnCl_2$ =1:1:2:2. In these conditions the yields becomes 83% for 9 min of irradiation.

In classical reaction conditions the synthesis of 9-ethylacridine doesn't occur very well. By convention heating of reagents on a oil bath the yields is only 18% for 10 hat 140°C (entry 9, table 1). The excess of propionic acid or aromatic amine doesn't increase the yield of reaction.

Increasing the amount of carboxylic acid (entry 8, table 1) produce a better yield than increasing the amount of amine (entry 7, table 1). The carboxylic acid absorbs microwaves better than amine in the reaction medium and the yield is higher. Increasing the irradiation time, when the ratio of reactants is optimal, does not improves the yield of reaction.

The optimal parameters for the synthesis of 9-ethylacridine were used as starting point to obtain several acridine derivatives. The structure of the product are reported in table 2.

Bernthsen's acridine synthesis takes place by an electrophilic substitution mechanism. The electrophilic reagent is acyl cation $ArCO^+$. It results from carboxylic acid and $ZnCl_2$ and attack the ortho position from diphenylamine. DMP captures the water molecules and allows easier regeneration of the catalyst and increases its activity. This mechanism of Bernthsen reaction was previously presented [22] and is depicted as bellow:

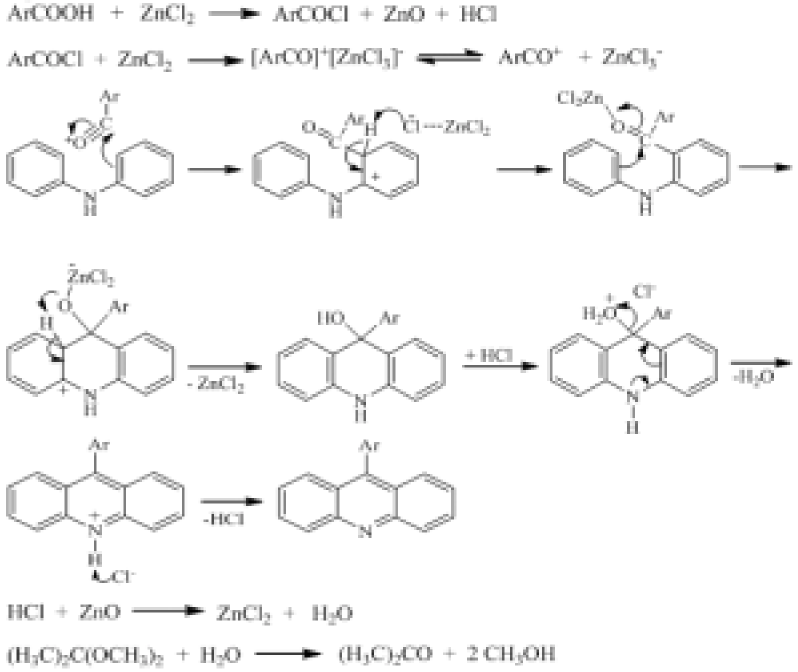
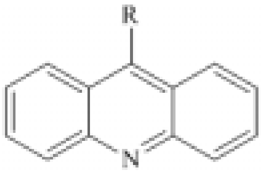
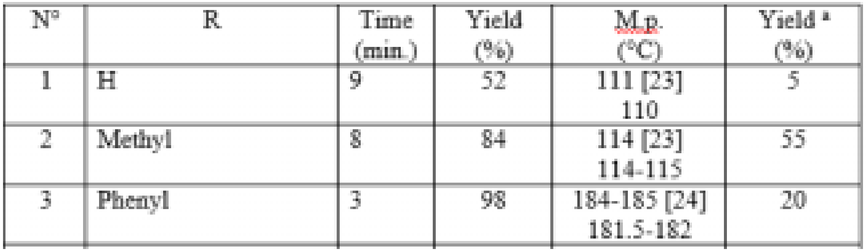


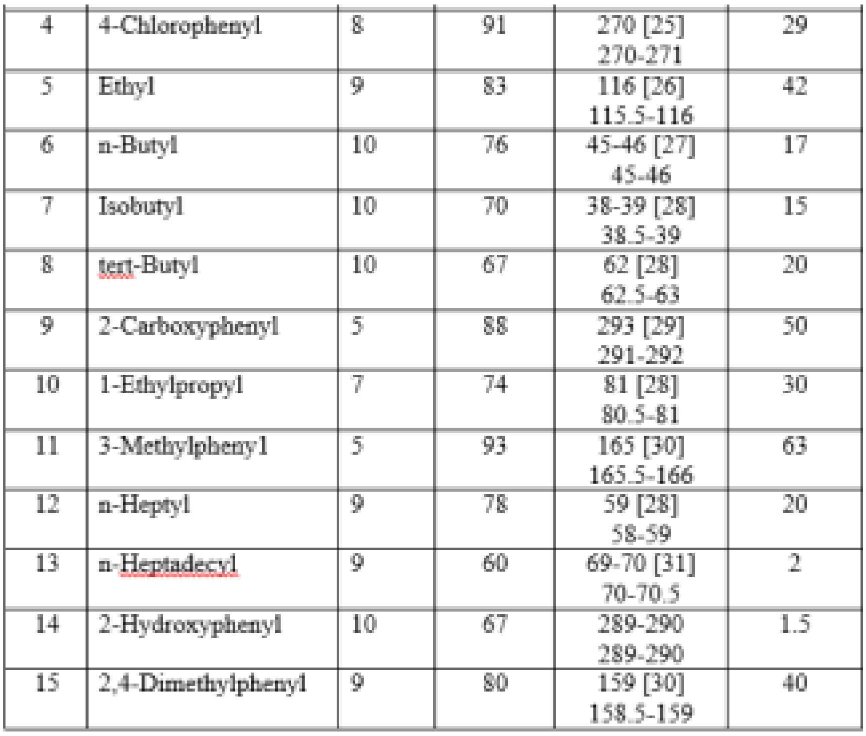
Table 2
SYNTHESIS OF 9-SUBSTITUTED-ACRIDINES BY AN ECO-FRIENDLY METHOD





N°	R	Time (min.)	Yield (%)	M.p. (°C)	Yield ^{a} (%)
1	H	9	52	111 [23] 110	5
2	Methyl	8	84	114 [23] 114-115	55
3	Phenyl	3	98	184-185 [24] 181.5-182	20

Table 2
CONTINUATED



4	4-Chlorophenyl	8	91	270 [25] 270-271	29
5	Ethyl	9	83	116 [26] 115.5-116	42
6	n-Butyl	10	76	45-46 [27] 45-46	17
7	Isobutyl	10	70	38-39 [28] 38.5-39	15
8	tert-Butyl	10	67	62 [28] 62.5-63	20
9	2-Carboxyphenyl	5	88	293 [29] 291-292	50
10	1-Ethylpropyl	7	74	81 [28] 80.5-81	30
11	3-Methylphenyl	5	93	165 [30] 165.5-166	63
12	n-Heptyl	9	78	59 [28] 58-59	20
13	n-Heptadecyl	9	60	69-70 [31] 70-70.5	2
14	2-Hydroxyphenyl	10	67	289-290 289-290	1.5
15	2,4-Dimethylphenyl	9	80	159 [30] 158.5-159	40

^{a} - Conventional synthesis

Reactions of obtaining acridine derivatives from diphenyamine and aromatic acids occur better than reactions involving aliphatic acids. 9-Phenylacridine is *obtained* in *quasi-quantitative* yield (entry 3, table 2).

Conclusions

Acridines can be obtained by an eco-friendly method using a free medium solvent and a water scavenger 2,2-dimethoxypropane. The time is bellow 10 min and the *reactions* of condensations *run* with a good yield. In some cases, the acridines are *quasi-quantitatively* obtained. The consumption of reagents, amines and carboxylic acids is optimal. At the end of synthesis, the acridine derivatives are easily separated from the mixture and heavy processes of removal and purification of products were no longer required. The rate of reaction is very high when using microwaves heating source. Additionally, the energy consumption is considerably diminished.

References

1. SU, T.L., LIN, Y.W., CHOU, T.C., ZHANG, X., BACHERIKOV, V.A., CHEN, C.H., LIU, L.F., TSAI, T.J., J. Med. Chem., **49**, 2006, p.3710
2. MISSAILIDIS, S., STANSLAS, J., MODI, C., ELLIS, M.J., ROBINS, R.A., LAUGHTON, C.A., STEVENS, M.F.G., Oncol. Res., **13**, 2002, p.175.
3. FINLAY, G.J., BAGULEY, B.C., Cancer Chemoth. Pharm., 2000, **45**, p. 417.
4. BELMONT, P., BOSSON, J., GODET, T., TIANO, M., Anticancer Agents Med Chem., **7**, 2007, p. 139.
5. GOODELL, J.R., PUIG-BASAGOITI, F., FORSHEY, B.M., SHI, P.Y., FERGUSON, D.M., J. Med. Chem., **49**, 2006, p. 2127.
6. SONDHI, S.M., BHATTACHARJEE, G., JAMEEL, R.K., SHUKLA, R., RAGHUBIR, R., LOZACH, O., MEIJER, L., Cen. Eur. J. Chem., **2**, 2004, p.1
7. DI GIORGIO, C., DE MEO, M., CHIRON, J., DELMAS, F., NIKOYAN, A., JEAN, S., DUMENIL, G., TIMON-DAVID, P., GALY, J.P., Bioorg. Med. Chem., **13**, 2005, p. 5560.
8. ZANJANIA, N.T., , SAIRIA, F., MARSHALLA, G., SAKSENAB, M.M., VALTCHEVA, P., GOMESA, V. G., CUNNINGHAMB, A. L., DEHGHANI, F., Eur. J. Pharm. Sci., **53**, 2014, p. 77.
9. IPPOLITO, A., Curr. Med. Chem., **21**, 2014, p. 1701.
10. THIAGARAJAN, V., SELVARAJU, C., RAMAMURTHY, P., J. Photochem. Photobiol. A, **157**, 2003, p. 23.
11. WANG, M., YANG, J., WU, X., HUANG, F., Anal. Chim. Acta, **422**, 2000, p. 151.
12. ALBERT, A., The Acridines, St. Martin's Press, New York, 1966, pp. 403-504.
13. THOMAS, A. M., SUJATHA A., ANILKUMAR, G., Mini-Rev. Org. Chem., **11**, 2014, p.3.
14. SEKHAR, B.C., J. Heterocycl. Chem., **41**, 2004, p. 807.
15. BELMONT, P., ANDREZ, J.C., ALLAN, C.S.M., Tetrahedron Lett., **45**, 2004, p. 2783.
16. DAS, S., THAKUR, A.J., Green Chem. Lett. Rev., **2**, 2011, p. 131
17. MAJUMDER, A., GUPTA, R., JAIN, A., Green Chem. Lett. Rev, **6**, 2013, p.151.
18. BRATULESCU, G., Heterocycles, **89**, 2014, p. 1877.
19. ZANG, H., ZHANG, Y. , MO, Y., CHENG, B., Synth. Commun., **41**, 2011, p. 3207.
20. POPP, F.D., J. Org. Chem., **27**, 1962, p. 2658.
21. JOSEPH, J., KURUVILLA, E., ACHUTHAN, A.T., RAMAIAH, D., SCHUSTER, G.B., Bioconj. Chem., **15**, 2004, p. 1230
22. BRATULESCU, G., Curr. Org. Synth., **10**, 2013, p.947.
23. BERNTHSEN, A., Justus Liebigs Ann. Chem., **1**, 1884 ,p. 224.
24. STASKUN, B., J. Org. Chem., **29**, 1964, p. 2856.
25. DUNSTAN A. E., HILDITCH, T. P., J. Chem. Soc., **91**, 1907, p. 1659
26. TSUGE, O., NISHINOHARA, M., SADANO, K., Bull. Chem. Soc. Jap., **38**, 1965, p. 2037.
27. BERNTHSEN, A., TRAUBE, J., Chem. Ber., **17**, 1884, p. 1510.
28. BUU-HOI, N. P., LECOCQ, J., Rec. Trav. Chim. Pays-Bas, **64**, 1945, p. 250.
29. DECKER, H., HOCK, T., Chem. Ber., **37**, 1904, p. 1002.
30. SCHMID, A., DECKER, H., Chem. Ber., **39**, 1906, p. 933.
31. VOLPI, A., Chem. Ber., **25**, 1892, p. 940.
32. LANDAUER, E., Bull. Soc. Chim. Fr., **31**, 1904, p. 1083.

Manuscript received: 8.01.2015