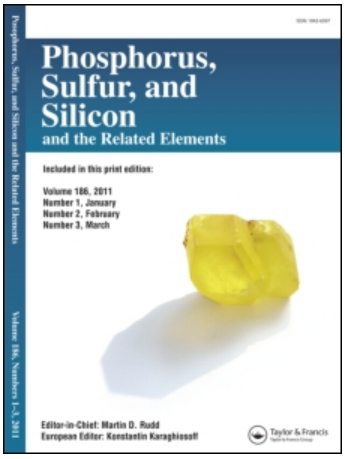

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Microwave-Assisted Synthesis of Quinoxalines, Benzoxazines, and Benzothiazines Under Solvent-Free Conditions

Majid M. Heravi[a]; Navabeh Nami[a]; Hossien A. Oskooie[a]; Rahim Hekmatshoar[a]
[a] Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran

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Majid M. Heravi
Navabeh Nami
Hossien A. Oskooie
Rahim Hekmatshoar
Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran

The addition of dialkyl acetylenedicarboxylate to o-phenylenediamine, o-aminophenol, and o-aminothiophenol under microwave irradiation in solventless system rapidly afforded quinoxaline, benzoxazine, and benzothiazine derivatives, respectively.

Keywords Benzothiazine; benzoxazine; dialkyl acetylenedicarboxylate; quinoxaline

Quinoxalines, benzoxazines, and benzothiazines have served as a rich source of variety of pharmaceutical agents and biological properties.[1–11] These compounds represent an important class of nitrogen heterocycles and they constitute useful intermediates in organic syntheses.[12] Acetylenic esters have proven to be very versatile reagents for heterocyclization and many diverse products can be prepared from the addition of these compounds to nitrogen-, oxygen-, and sulfur-containing compounds.[13,14]

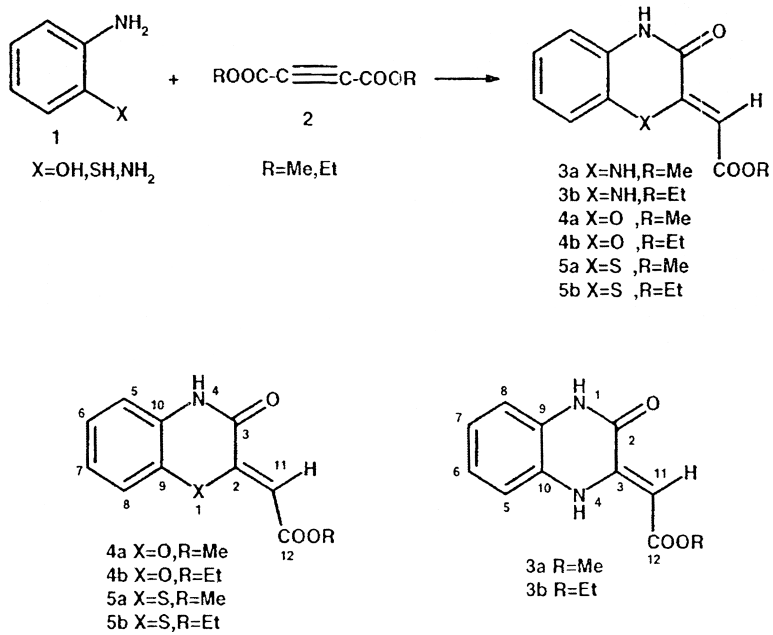
The microwave-enhanced chemical reactions[15] have gained popularity over the usual homogeneous and heterogeneous reactions as they can be conducted rapidly and pure products are obtained in high yields in a solvent-free condition. Organic solvents are not only expensive, they are also hazardous and flammable.[16]

We are interested in the chemistry of heterocyclic compounds containing nitrogen and sulfur atoms.[17] We are also interested in microwave-assisted organic reaction in a solventless system.[18] As a

Received June 6, 2004; accepted September 7, 2004.
Address correspondence to Majid M. Heravi, Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran. E-mail: mmheravi@azzahra.ac.ir

part of a research program on the synthesis of heterocyclic system containing nitrogen and sulfur in solventless system under microwave irradiation and with a view to extending the synthetic utility of dialkyl acetylendicarboxylate,[19] we have investigated the addition of the latter to o-phenylenediamine **1** (X=NH_2), o-aminophenol **1**(X=OH), and o-aminothiophenol **1**(X=SH) under microwave irradiation in a solventless system. The reactions were simply conducted by mixing of **1**(X=NH_2) with dialkyl acetylenedicarboxylate **2** (R=Me or Et) in a beaker and placing the beaker in microwave oven for a short period of time. The progress of the reaction was monitored by TLC using methanol and chloroform as an eluent. As long ago as 1975,[20c] the product from o-phenylenediamine and dimethyl acetylenedicarboxylate was formulated as **3a** (Scheme 1). Our product showed the same physical and spectroscopic data. It showed IR absorption at 1688 (ester C=O str), 1635 (amide C=O str), and 813 cm^{-1} (trisubstituted C=C), which has been formulated as 3,4-Dihydro-3-(methoxycarbonylmethylene) quinoxaline-2(1H) one (**3a**).[20]

We also used diethyl acetylenedicarboxylate (**2**, R=Et) to obtain the different substituted 3,4-dihydro-3-(ethoxycarbonylmethylene) quinoxaline-2(1H)-one (**3b**).[20]



SCHEME 1

To establish the generality of method, o-aminophenol **1**(X=OH) and o-aminothiophenol **1**(X=SH) were reacted in the same manner with dialkyl acetylendicarboxylate (**2**, R=Me or Et) to obtain 2-substituted carbonylmethylene-3,4-dihydro-2H-1,4-benzoxazine-3-one (**4a, b**)[21] and 2-substituted carbonylmethylene-3,4-dihydro-2H-1,4-benzothiazine-3-one (**5a**, **b**).[22]

In conclusion, the solvent-free microwave thermolysis is a convenient, rapid, high-yielding and environmental friendly protocol for the synthesis of quinoxaline, benzoxazine, and benzothiazines when compared with conventional reaction in a solution phase.

EXPERIMENTAL

The melting points were obtained using an Electrotermal IA 9100 Digital Melting Point. The IR spectra were recorded on a 4300 Shimadzu spectrometer. NMR spectra were recorded on a 500 MHZ spectrometer using TMS as internal standard. The mass spectra were recorded on an Agilent Technologies 6890 N Network GC System. Microwave oven LG Combi was used for all reactions.

SYNTHESIS OF QUINOXALINE, BENZOXAZINE, AND BENZOTHIAZINE

General Procedure

Compound **1**(X=NH, OH, SH), (1 mole) was mixed with **2** (R=Me or Et), (1 mole) thoroughly in a beaker. The beaker was placed in a microwave oven for 5 min (900 W). The progress of reaction was monitored by TLC, using methanol:chloroform (9:1) in eluent. The crude product was crystallized from the suitable solvent. The selected physical and spectroscopic data are given below.

3,4-Dihydro-3-(methoxycarbonylmethylene)-quinoxaline-2(1H)-one (3a)

Mp = 227°C from MeOH (Lit[20].227°C), yield 90%. IR (KBr) ($\upsilon_{max,}$cm^{-1}): 3259 (NH amide), 3203 (NH), 3047 (Ar—H), 3010 (=CH), 2888 (R—H), 1688 (CO ester), 1635 (CO amide), 1504 (C=C), 1434 (C=C), 1394, 1334, 1267, 1217, 1132, 1029, 813 (C=C trisubstituted), 741, 691. MS, m/z (%); 218(M^+, 100), 203(54), 189(10), 175(65), 109(8), 77(5), 63(7), 44(10), 32(10).

3,4-Dihydro-3-(ethoxycarbonylmethylene)quinoxaline-2(1H)-one (3b)

Mp = 218°C from EtOH (Lit[20]·218°C), yield 85%. ^{1}H-NMR ($CDCl_3$)δ 1.22(t, $J = 7.5$, 3H, CH_3), 4.13(q, $J = 7.5$, 2H, OCH_2), 5.48(s, 1H, =CH), 7.03(m, 3H, benzene hydrogen), 7.05(d, 7.6, 1H, benzene hydrogen), 11.04(s, 1H, NH), 11.70(s, 1H, NH). IR (KBr) (υ_{max}, cm^{-1}): 3250(NH amide), 3130(NH), 3020 (Ar—H), 2960(R—H), 1677(CO ester), 1630(CO amide), 1608(C=C), 1475(C=C), 1427, 1380, 1268, 1215, 1150.

2-Methoxycarbonylmethylene-3,4-dihydro-2H-1,4-benzoxazine-3-one (4a)

Mp = 150°C from MeOH (Lit[21]·150°C), yield 75%.^{1}H-NMR ($CDCl_3$)δ 3.68(s, 3H, CH_3), 5.60(s, 1H, =CH), 7.01 (m, 3H, benzene hydrogen), 7.48(s, 1H, benzene hydrogen), 10.65(s, 1H, NH).^{13}C-NMR ($CDCl_3$) δ 51.53(CH_3), 88.76(C-11), 116.47(C-5), 116.72(C-6), 122.92(C-7), 125.06(C-8), 125.66(C-10), 139.19 (C-9), 140.34(C-2), 156.38(C-3), 169.01(C-12). IR (KBr) (υ_{max}, cm^{-1}): 3332(NH amide), 3029(Ar—H), 2951(R—H), 1766(CO ester), 1729, 1621(CO amide), 1500(C=C), 1445(C=C), 1376, 1286, 1227, 1118, 1020, 755, 685cm.MS, m/z (%): 219(M^+,68),187(77),159(100), 132(78), 103(32), 77(23), 63(18), 44(13), 32(34).

2-Ethoxycarbonylmethylene-3,4-dihydro-2H-1,4-benzoxazine-3-one (4b)

Mp = 97°C from EtOH (Lit[21]·97°C), yield 84%.^{1}H-NMR ($CDCl_3$)δ 1.32(t, $J = 7.2$, 3H, CH_3), 4.24 (q, $J = 7.2$, 2H, OCH_2), 5.93 (s, 1H, =CH), 7.01 (m, 2H, benzene hydrogen), 7.14 (m, 2H, benzene hydrogen), 10.69(s, 1H, NH). IR (KBr) (ν_{max}, cm^{-1}): 3263(NH amide), 3015(Ar-H), 2981(R—H), 1762(CO ester), 1659 (CO amide), 1619(C=C), 1493(C=C), 1443, 1369, 1287, 1118, 1033, 923, 758, 685. MS, m/z (%): 233(M^+, 70), 205(6), 187(98), 159(100), 132(23), 103(27), 77(12), 3(10), 52(6).

2-Methoxycarbonylmethylene-3,4-dihydro-2H-1,4-benzothiazine-3-one (5a)

Mp = 264°C from MeOH (Lit[22].264–266°C), yield 94%.^{1}H-NMR (DMSO)δ 3.65(s, 3H, CH_3), 6.88(s, 1H, =CH), 7.05 (t, $J = 7.8$, 1H, benzene hydrogen), 7.10(d, $J = 7.8$, 1H, benzene hydrogen), 7.21 (t, $J = 7.8$, 1H, benzene hydrogen), 7.38(d, $J = 7.8$, 1H, benzene hydrogen), 11.52 (s, 1H, NH). ^{13}C-NMR (DMSO) δ 52.18(CH_3), 114.15(C-11), 115.46(C-5),

117.53(C-6), 123.87(C-7), 125.66(C-8), 127.68(C-10), 135.50(C-9), 141.52(C-2), 154.62(C-3), 166.34(C-12). IR(KBr) ($\upsilon_{max,}$ cm^{-1}): 3180(NH amide), 3039(Ar-H), 2972(RH), 1667(CO ester), 1667(CO amide), 1559(C=C), 1500(C=C), 1431, 1376, 1311, 1197, 1025, 859, 745. MS, m/z (%): 235(M^+, 100), 204(34), 175(48), 148(30), 121(9), 103(6), 77(6), 53(5), 64(3).

2-Ethoxycarbonylmethylene-3,4-dihydro-2H-1,4-benzothiazine-3-one (5b)

Mp = 221°C from EtOH (Lit[22].220–222°C), yield 96%.^{1}H-NMR (DMSO)δ 1.22(t, $J = 7$, 3H,CH_3),3.31(q, $J = 7$, 2H, OCH_2),6.88(s, 1H, =CH),7.05(t, $J = 7.7$, 1H, benzene hydrogen), 7.11(d, $J = 7.7$,1H, benzene hydrogen),7.23(t, J = 7.7, 1H, benzene hydrogen),7.40(d, J = 7.7, 1H, benzene hydrogen), 11.52(s, 1H, NH). IR (KBr) (υ_{max}, cm^{-1}): 3265 (NH amide), 3045(Ar–H), 2979 (R–H), 1663 (CO ester), 1663 (CO amide), 1560(C=C), 1369, 1307, 1194, 1035, 859, 750.MS, m/z (%): 249(M^+, 100), 235(9), 221(7), 204(45), 177(55), 148(37), 121(9), 104(7), 77(6), 63(5), 53(5).

CAUTION

Although we did not have an accident, using a microwave oven and an efficient hood is highly recommended.

REFERENCES

[1] C. F. Turk, J. Krapecho, I. M. Michael, and I. Weinryb, *J. Med. Chem.*, **20,** 729 (1977).
[2] G. Thuiler, J. Laforest, P. Bessim, and J. Thuillier, *Eur. J. Med. Chem.*, **10,** 37 (1975).
[3] A. S. Bourlot, I, Sanchez, G. Dureng, G. Guillaumeat, R. Masingham, A. Monteil, E. Winslow, M. D. Pujol, and J. Y. Merour, *J. Med. Chem.*, **41,** 3142 (1998).
[4] A. P. Kozikowski, K. Sugiyama, and J. P. Springer, *J. Org. Chem.*, **46,** 2428 (1981).
[5] M. Kajino, Y. Shibuta, K. Nishikava, and K. Meguro, *Chem. Pharm. Bull*., **39,** 2896 (1991).
[6] E. D. Brock, D. M. Lewis, F. T. I. Yousa, and H. H. Harper, *The Procter and Gamble Company, USA WO 9951688* (1999).
[7] A. Gazit, H. App, G. Memahon, S. J. Chen, A. Levitzki, and F. D. Bohmer, *J. Med. Chem.,* **39,** 2170 (1996).
[8] U. Schlstedt, P. Aich, J. Bergman, H. Vallberg, B. Novden, and U. A. Graslund, *J. Mol. Biol.*, **278,** 31 (1998).
[9] S. Dailey, J. W. Feast, R. J. Peace, I. C. Sage, S. Till, and E. L. Wood, *J. Mater. Chem.*, **11,** 2238 (2001).
[10] R. F. Borne, Nonsteroidal Anti in Flammatory Drugs, in *Principles of Medical Chemistry* (Eds, W. O. Foye, T. L. Kemke, and D. A. Williams), Williams and Wilkins, Philadelphia, CA pp. 535–580. (1995).

[11] J. G. Lombardino, Benzothiazine Dioxide Derivatives, *U.S. Pat. Us 4, 309, 427, 05 Jan1982; Ref. Chem. Abstr.*, **96,** 122810s (1982).
[12] R. M. Acheson and N. F. Elmor, *Adv Heterocyclic Chem.,* **23,** 263 (1978).
[13] I. Yavari, M. T. Maghsoodlu, and A. Pourmossavi, *J. Chem. Res.,* **5,** 212 (1997).
[14] F. Barka and B. Batanero, *Synthesis,* **5,** 55 (1994).
[15] K. Tanaka and F. Toda, *Chem. Rev,* **100,** 1025 (2000).
[16] C. B. Khour, C. B. Darth, A. Lalnger, and M. E.Daves, *J. Catal*, **149,** 195, (1994).
[17] (a) M. M. Heravi and M. Bakavoli, *J. Chem, Res*, **11,** 480 (1995); (b) M. M. Heravi, Z. Tavaliee, and O. Sabzevari, *Ind. J. Chem. Sect, B,* **37b,** 585 (1998); (c) M. M. Heravi, H. A. Oskooie, and M. Mafi, *Synth Commun.,* **27,** 1725 (1997); (d) M. M. Heravi, G. H. Rajabzadeh, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *Phosphorus, Sulfur and Silicon,* **174,** 129 (2001); (e) M. M. Heravi, N. Montazeri, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *J.Chem.Res*, 584 (2000); (f) M. M.Heravi, N. Montazeri, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *Monatsh Chem,* **132,** 1225 (2001); (g) M. M. Heravi, A. Kivanloo, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *Tetrahedron Lett.*, **45,** 5747 (2004).
[18] (a) M. M. Heravi, D. Ajami, and M. Ghassemzadeh, *Synthesis,* **3,** 393 (1999); (b) M. M. Heravi, D. Ajami, K. Aghapour, and M. Ghassemzadeh, *J. Chem. Soc. Chemical Communication*, 833 (1999); (c) M. M. Heravi, D. Ajami, M. M. Mojtahedi, and M. Ghassemzadeh, *Tetrahedron Lett.,* **40,** 561 (1999); (d) M. M. Heravi, M. Tajbakhsh, S. Habibzadeh, and M. Ghassemzadeh, *Phosphorus, Sulfur*, *and Silicon*, **177,** 2299 (2002).
[19] (a) M. M. Heravi,Y. Sh. Beheshtiha, N. Nami, and M. Ghassemzadeh, *Phosphorus, Sulfur and Silicon*, **161**, 7 (2000); (b) M. M. Heravi, Y. Sh. Beheshtiha, N. Nami, and R. Hekmatshoar, *Phosphorus, Sulfur and Silicon*, **165, 285,** (2000).
[20] (a) Y. Kurasawa, A. Takano, K. Kato, and A. Takada, *J. Heterocycl. Chem.*, **33,** 421 (1996); (b) R. M. Acheson and J. D Wallis, *J. Chem. Soc. Perkin I*, 415 (1981); (c) H. Suschitzky, B. J. Wakefield, and R. A. Whittaker, *J.Chem.Soc.Perkin* **I,** 401 (1975); (d) Y. Iwanami, *Nippon Kagaku Zasshi*, **82,** 778 (1961).
[21] (a) N. Mohann D., *Indian J. Chem*. 7, 229 (1969); (b) Y. Iwanami, Yasuo, *Bull. Chem. Soc. Jap.,* **44,** 1311 (1971).
[22] (a) S. M. Kalbag, M. D. Nair, P. Rajagopalan, and C. N. Talatyy, Tetrahedron, **23,** 1911 (1967); (b) L. K. Mushkalo, and V. A. Bezemskaya, *Ukrain. Khim. Zhur*, **18,** 163 (1952); (c) Y. Iwanami, *Nippon Kagaku Zasshi*, **83,** 100 (1962).