One-pot Synthesis of Hexahydroquinolines *Via* a Four-component Cyclocondensation under Microwave Irradiation in Solvent Free Conditions: a Green Chemistry Strategy

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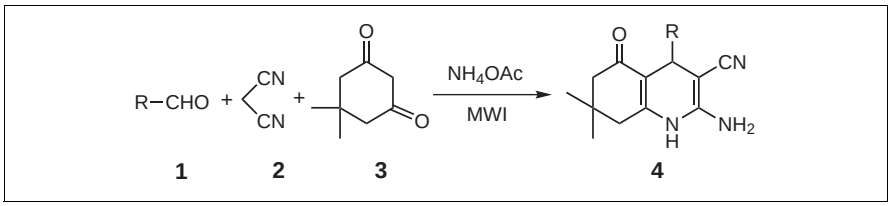

Four-component cyclocondensation of aromatic aldehydes, malononitrile, dimedone and ammonium acetate proceeds under microwave irradiation in solvent free conditions to give highly functionalized hexahydroquinolines in excellent yields.

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Introduction.

Green chemistry is an environmental, health and safe strategy that emphasizes pollution prevention and application of chemical process to reduce or eliminate the use and generation of hazardous substance.

Development of new solid phase (solvent free) reactions and transferring solution phase reactions to solid phase are subjects of recent interest in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimization of drug candidates [1]. One-pot multi-component reactions (MCRs) by virtue of their convergence, productivity, facile execution and generally high yield of products have attracted considerable attention from the point of view of ideal synthesis [2]. In the past decade there have been tremendous developments in three- and four-component reactions and great efforts have been and still are being made to find and develop new MCRs [3]. Microwave-promoted solvent-free reactions are well known as environmentally benign methods that also usually provide improved selectively, enhanced reaction rates, cleaner products and manipulative simplicity [4].

1,4-Dihydropyridines (1,4-DHPs) are well-known compounds as a consequence of their pharmacological profile as the most important calcium channel modulators [5]. The chemical modifications of the DHP ring such as the introduction of different substituents or heteroatoms [6] have allowed expansion of the research to structure-activity relationship to afford new insight into the molecular interactions at the receptor level. In fact, it is well-established that slight structural modification on the DHP ring may bring significant change in pharmacological activities [7]. Many heterocyclic compounds having a 1,4-dihydropyridine nucleus are also known to have a wide range of biological activities [8]. Quinolines having a 1,4-dihydropyridine nucleus are very important compounds because of their pharmacological properties. Members of this family have wide applications in medicinal chemistry, being used as antimalarial, anti-inflammatory, antiasthamatic, antibacterial antihypertensive, and tyrosine kinase inhibiting agents [9-11].

Recently, Margarita Suárez reported the synthesis of 1,4,5,6,7,8-hexahydroquinolines by refluxing equimolar amounts of the corresponding arylidenemalononitrile, dimedone and excess of ammonium acetate in acetic acid as solvent [12]. However, in this reaction, the use of arylidenemalononitrile which should be first synthesized from aldehyde and malononitrile makes the work-up procedure complicated and leads to poor total yields of the products. To top it off, using organic solvent like acetic acid will pollute the environment. As part of our continued interest [13] in the development of highly expedient and environmentally benign methods for the synthesis of heterocyclic compounds of biological importance, we report here a very simple and highly efficient method for the synthesis of 1,4,5,6,7,8-hexahydroquinolines *via* a four-component cyclocondensation reaction using raw materials under microwave irradiation in solvent free conditions (Scheme 1). The procedure not only gives products in good yields, but avoids problems connected with solvent use (cost, handling, safety, and pollution), and moreover, the route is shortened and the reaction time is reduced from several hours to a few minutes.

Results and Discussion.

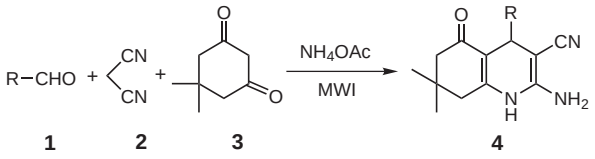
The results (Table 1) show that different kinds of aldehydes including aromatic aldehyde and heterocyclic aldehyde can give excellent yields (80-94%) of the products under the cyclocondensation. All the products are characterized by IR, ^{1}H NMR. And the elemental analyses of these compounds are in agreement with their structures. Furthermore, the structure of **4a** was established by an X-ray crystallographic analysis (Figure 1) [14].

Table 1

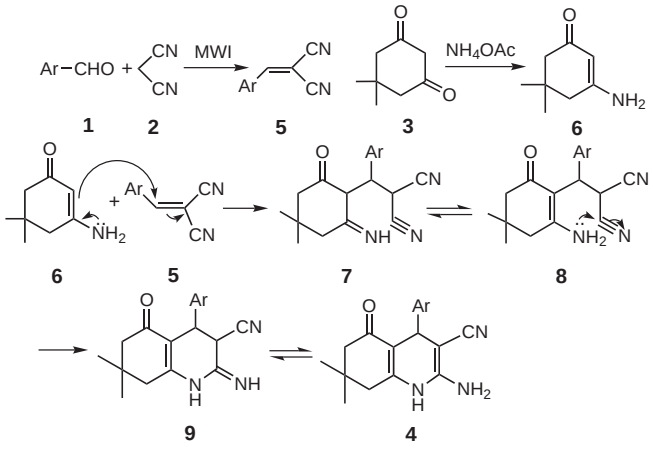
The synthesis of 4 under microwave irradiation

Entry	R^1	Time Min (lit.)	Yield % (lit.)	Mp (°C)
4a	C_6H_5	6	90(70)[12]	280-281(237-238)[12]
4b	4-OCH_3-C_6H_4	8	88(65)[12]	288-289(204-206)[12]
4c	4-$N(CH_3)_2$-C_6H_4	8	80(65)[12]	>300(224-226)[12]
4d	3-NO_2-C_6H_4	6	88(70)[12]	282-283(197-198)[12]
4e	2,4-Cl_2-C_6H_3	8	90(74)[12]	>300(190-192)[12]
4f	4-F-C_6H_4	6	88	299-300
4g	3,4-Cl_2- C_6H_3	7	90	>300
4h	2,3-$(CH_3O)_2$-C_6H_3	8	82	269-270
4i	4-Cl-C_6H_4	8	92	290-291
4j	4-Br-C_6H_4	8	94	295-296
4k	3,4-OCH_2O-C_6H_3	7	92	>300
4l	4-CH_3-C_6H_4	8	84	>300
4m	2-C_4H_3S	7	80	256-257

Scheme 1



Scheme 2



A mechanism for the reaction is outlined in Scheme 2. The reaction may be *via* initial formation of the arylidenemalononitrile **5** from the condensation of aromatic aldehyde **1** and malononitrile **2**. Then **5** reacts with **6** (from dimedone and ammonium acetate) to give the intermediate **7**, which isomerizes to **8**. After that, **8** cyclizes to afford **9**, which isomerizes to the desired compound **4**. The efficiency of the current solid-state procedure may be ascribed to an enhanced reaction rate resulting from ultimately concentrations of reactants with no use of solvent and the promotion of microwave irradiation. In addition, we find the melting points of **4a**-**4e** are much higher than those reported [12] due to the dimerization of the molecules [14].

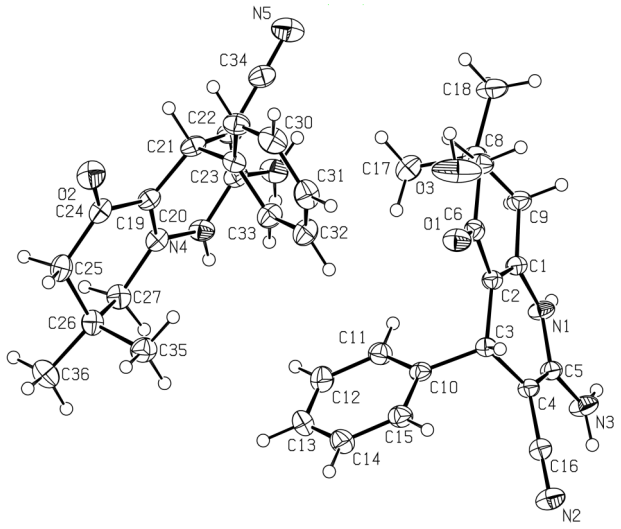


Fig 1 X-ray structure of **4a**

In summary, we have developed a novel, one-pot, four-component reaction under microwave irradiation in solvent free conditions that offers a simple, efficient and environmentally benign route for the synthesis of 1,4,5,6,7,8-hexahydroquinolines exhibiting biological importance in good to excellent yields.

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EXPERIMENTAL

Microwave irradiation was carried out in a modified commercial microwave oven (2450 MHz, Nanjing Sanle) under atmospheric pressure. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Shimadzu spectrometer. ^{1}H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-*d6* as solvent and TMS as internal standard. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument.

General Procedure for 1,4,5,6,7,8-Hexahydroquinolines.

A dry flask (25 mL) was charged with equimolar amounts of aromatic adehyde, malononitrile, dimedone and excess of ammonium acetate. The flask was then connected to refluxing equipment. After microwave irradiation for 6-8 min., the reaction mixture was cooled and poured into water the solid product was collected by filtration and washed with water. The crude solid was purified by recrystallisation from EtOH to afford the 1,4,5,6,7,8-hexahydroquinoline **4**.

2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4a**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3426, 3315 and 3205 (NH and NH_2), 2175 (CN), 1654 (C=O), 1604 (C=C) cm^{-1}; ^{1}H NMR: δ 8.88 (1H, s, NH) , 7.15-7.24 (5H, m, ArH), 5.73 (2H, s, NH_2), 4.31 (1H, s, CH), 2.42 (1H, d, J = 16.8 Hz, CH_2), 2.30 (1H, d, J = 16.8 Hz, CH_2), 2.18 (1H, d, J = 16.0 Hz, CH_2), 1.98 (1H, d, J = 16.0 Hz, CH_2), 1.02(3H, s, CH_3), 0.91(3H, s, CH_3).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32; Found C, 73.88; H, 6.41; N, 14.56.

2-Amino-4-(4'-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4b**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3389, 3328 and 3222 (NH and NH_2), 2180 (CN), 1657 (C=O), 1599 (C=C) cm^{-1}; ^{1}H NMR: δ 8.81 (s, 1H, NH), 7.03 (d, 2H J = 8.0 Hz, ArH), 6.80 (d, 2H, J = 8.0 Hz, ArH), 5.68 (s, 2H, NH_2), 4.26 (s, 1H, CH), 2.41 (d, 1H, J = 16.8 Hz, CH_2), 2.28 (d, 1H, J = 16.8 Hz, CH_2), 2.17 (d, 1H, J = 16.0 Hz, CH_2), 1.98 (d, 1H, J = 16.0 Hz, CH_2), 1.02 (s, 3H, CH_3), 0.91 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99; Found C, 70.50; H, 6.41; N, 13.11.

2-Amino-4-(4'-*N*,*N*-dimethylaminophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4c**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3388, 3328 and 3224 (NH and NH_2), 2180 (CN), 1655 (C=O), 1599 (C=C) cm^{-1}; ^{1}H NMR: δ 8.81 (s, 1H, NH), 6.94 (d, 2H, J = 8.0 Hz, ArH), 6.64 (d, 2H, J = 8.0 Hz, ArH), 5.60 (s, 2H, NH_2), 4.20 (s, 1H, CH), 2.84 (s, 6H, $N(CH_3)_2$), 2.31 (d, 1H, J = 16.8 Hz, CH_2), 2.18 (d, 1H, J = 16.8 Hz, CH_2), 2.07 (d, 1H, J = 16.0 Hz, CH_2), 1.92(d, 1H, J = 16.0 Hz, CH_2), 1.02(s, 3H, CH_3), 0.91(s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{24}N_4O$: C, 71.40; H, 7.19; N, 16.65; Found C, 71.57; H, 7.10; N, 16.78.

2-Amino-4-(3'-nitrophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4d**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3392, 3330 and 3222 (NH and NH_2), 2178 (CN), 1658 (C=O), 1599 (C=C) cm^{-1}; ^{1}H NMR: δ 9.04 (s, 1H, NH), 8.04 (d, 1H, J = 7.6 Hz, ArH), 7.93 (s, 1H, ArH), 7.64-7.57 (m, 2H, ArH), 5.94 (s, 2H, NH_2), 4.50 (s, 1H, CH), 2.46 (d, 1H, J = 17.2 Hz, CH_2), 2.35 (d, 1H, J = 17.2 Hz, CH_2), 2.20 (d, 1H, J = 16.0 Hz, CH_2), 2.00 (d, 1H, J =16.0 Hz, CH_2), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56; Found C, 63.99; H, 5.21; N, 16.42.

2-Amino-4-(2',4'-dichlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4e**).

This compound was obtained according to above general procedure;ir (potassium bromide): 3410, 3325 and 3219 (NH and NH_2), 2185 (CN), 1663 (C=O), 1598 (C=C) cm^{-1}; ^{1}H NMR: δ 8.99 (s, 1H, NH), 7.39 (d, 1H, J = 8.8 Hz, ArH), 7.24 (d, 1H, J = 8.4 Hz, ArH), 7.10 (s, 1H, ArH) 5.86 (s, 2H, NH_2), 4.83 (s, 1H, CH), 2.46 (d, 1H, J = 17.6 Hz, CH_2), 2.37 (d, 1H, J = 17.6 Hz, CH_2), 2.20 (d, 1H, J = 16.4 Hz, CH_2), 2.00 (d, 1H, J = 16.4 Hz, CH_2), 1.03 (s, 3H, CH_3), 0.96 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{17}C_{l2}N_3O$: C, 59.68; H, 4.73; N, 11.60; Found C, 59.72; H, 4.71; N, 11.52.

2-Amino-4-(4'-fluorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4f**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3396, 3326 and 3223 (NH and NH_2), 2180 (CN), 1654 (C=O), 1590 (C=C) cm^{-1}; ^{1}H NMR: δ 8.91 (s, 1H, NH), 7.16-7.05 (m, 4H, ArH), 5.80 (s, 2H, NH_2), 4.32 (s, 1H, CH), 2.42 (d, 1H, J = 17.2 Hz CH_2), 2.31 (d, 1H, J = 17.2 Hz, CH_2), 2.17 (d, 1H, J = 16.0 Hz, CH_2), 1.99 (d, 1H, J = 16.0 Hz, CH_2), 1.01 (s, 3H, CH_3), 0.89 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{18}FN_3O$: C, 66.44; H, 5.83; N, 13.50; Found C, 66.56; H, 5.73; N, 13.33.

2-Amino-4-(3',4'-dichlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4g**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3403, 3325 and 3223 (NH and NH_2), 2180 (CN), 1665 (C=O), 1598 (C=C) cm^{-1}; ^{1}H NMR: δ 8.96 (s, 1H, NH), 7.53 (d, 1H, J = 8.4 Hz, ArH), 7.30 (s, 1H, ArH), 7.13 (d, 1H, J = 8.4 Hz, ArH), 5.86 (s, 2H, NH_2), 4.36 (s, 1H, CH), 2.42 (d, 1H, J = 17.2 Hz, CH_2), 2.34 (d, 1H, J = 17.2 Hz, CH_2), 2.18 (d, 1H, J = 16.0 Hz, CH_2), 2.01 (d, 1H, J = 16.0 Hz, CH_2), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{17}C_{l2}N_3O$: C, 59.68; H, 4.73; N, 11.60; Found C, 59.99; H, 4.66; N, 11.88.

2-Amino-4-(2',3'-dimethoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline(**4h**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3413, 3334 and 3222 (NH

and NH_2), 2172 (CN), 1665 (C=O), 1598 (C=C) cm^{-1}; ^1H NMR: δ 8.81 (s, 1H, NH), 6.92 (t, 1H, J = 8.2 Hz, ArH), 6.79 (d, 1H, J = 8.0 Hz, ArH), 6.60 (d, 1H, J = 8.0 Hz, ArH), 5.63 (s, 2H, NH_2), 4.73 (s, 1H, CH), 3.84 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 2.44 (d, 1H, J = 16.4 Hz, CH_2), 2.30 (d, 1H, J = 16.4 Hz, CH_2), 2.16 (d, 1H, J = 16.0 Hz, CH_2), 1.94 (d, 1H, J = 16.0 Hz, CH_2), 1.04 (s, 3H, CH_3), 0.95 (s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{23}N_3O_3$: C, 67.57; H, 6.56; N, 11.89; Found C, 67.64; H, 6.45; N, 11.66.

2-Amino-4-(4'-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4i**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3394, 3321 and 3223 (NH and NH_2), 2178 (CN), 1655 (C=O), 1601 (C=C) cm^{-1}; ^1H NMR: δ 8.90 (s, 1H, NH),7.31 (d, 2H, J = 8.0 Hz, ArH), 7.14 (d, 2H, J = 8.0 Hz, ArH), 5.78 (s, 2H, NH_2), 4.32 (s, 1H, CH), 2.42 (d, 1H, J = 16.8 Hz, CH_2), 2.31 (d, 1H, J = 16.8 Hz, CH_2), 2.17 (d, 1H, J = 16.0 Hz, CH_2), 1.99 (d, 1H, J = 16.0 Hz, CH_2), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{18}ClN_3O$: C, 69.95; H, 5.53; N, 12.82; Found C, 70.12; H, 5.41; N, 12.68.

2-Amino-4-(4'-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4j**).

This compound was obtained according to above general procedure; ir (potassium bromide): ν 3392, 3323 and 3223 (NH and NH_2), 2179 (CN), 1656 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR: δ 8.90 (s, 1H, NH), 7.44 (d, 2H, J = 8.0 Hz, ArH), 7.08 (d, 2H, J = 8.0 Hz, ArH), 5.78 (s, 2H, NH_2), 4.30 (s, 1H, CH), 2.42 (d, 1H, J = 16.8 Hz, CH_2), 2.31 (d, 1H, J = 16.8 Hz, CH_2), 2.17 (d, 1H, J = 16.0 Hz, CH_2), 1.99 (d, 1H, J = 16.0 Hz, CH_2), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{18}BrN_3O$: C, 58.08; H, 4.87; N, 11.29; Found C, 58.12; H, 4.88; N, 11.35.

2-Amino-4-(3',4'-methylenedioxylphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4k**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3410, 3323 and 3222 (NH and NH_2), 2182 (CN), 1640 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR: δ 8.83 (s, 1H, NH), 6.77-6.58 (m, 3H, ArH), 5.95 (s, 2H, OCH_2O), 5.71 (s, 2H, NH_2), 4.25 (s, 1H, CH), 2.40 (d, 1H, J = 16.8 Hz, CH_2), 2.32 (d, 1H, J = 16.8 Hz, CH_2), 2.17 (d, 1H, J = 16.0 Hz, CH_2), 2.01 (d, 1H, J = 16.0 Hz, CH_2), 1.02 (s, 3H, CH_3), 0.92 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46; Found C, 67.78; H, 5.58; N, 12.34.

2-Amino-4-(4'-methylphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4l**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3392, 3324 and 3223 (NH and NH_2), 2194 (CN), 1662 (C=O), 1601 (C=C) cm^{-1}; ^1H NMR: δ 8.82 (s, 1H, NH), 7.06 (d, 2H, J = 8.0 Hz, ArH), 7.02 (d, 2H, J = 8.0 Hz, ArH), 5.69 (s, 2H, NH_2), 4.26 (s, 1H, CH), 2.42 (d, 1H, J = 16.8 Hz, CH_2), 2.28 (d, 1H, J = 16.8 Hz, CH_2), 2.23 (s, 3H, CH_3), 2.16 (d, 1H, J = 16.0 Hz, CH_2), 1.96 (d, 1H, J = 16.0 Hz, CH_2), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67; Found C, 74.12; H, 6.71; N, 13.52.

2-Amino-4-(2'-thienyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**4m**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3378, 3321 and 3284 (NH and NH_2), 2198 (CN), 1677 (C=O), 1605 (C=C) cm^{-1}; ^1H NMR: δ 8.98 (s, 1H, NH), 6.85-7.12 (m, 3H, thiophene-CH), 5.85 (s, 2H, NH_2), 4.51 (s, 1H, CH), 2.29 (d, 1H, J = 16.8 Hz, CH_2), 2.20 (d, 1H, J = 16.8 Hz, CH_2), 2.14 (d, 1H, J = 16.0 Hz, CH_2), 2.06 (d, 1H, J = 16.0 Hz, CH_2), 1.01 (3H, s, CH_3), 0.92 (3H, s, CH_3).

Anal. Calcd. for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04; Found C, 64.33; H, 5.60; N, 13.89

REFERENCES AND NOTES

[1] T. Tanaka and F. Toda. *Chem. Rev*., **100**, 1025 (2000).

[2a] L. Weber, K. Illegen and M. Almstetter, *Synlett*, 366 (1999). [b] R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Rev*., **29**, 123 (1996).

[3a] A. Strecker, *Liebigs Ann. Chem*., **75**, 27 (1850). [b] S. Balalaie, M. Bararjanian, A. M. Amani, B. Movassagh *Synlett*, 263 (2006)

[4] S. A. Galema, *Chem. Soc. Rev*., **26**, 233 (1997).

[5a] J. H. Burkhalter and W. H. Edgerton, *J. Am. Chem. Soc*., **73**, 4837 (1951); [b] P. G. Bray and S. A. Ward, *Pharm. Therapeutics*, **77**, 1 (1998); [c] S. D. Sharad, E. S. Robert and A. Michael, *Toxicon*, **35**, 433 (1997); [d] G. Meilin, N. Tonglan, T. A. Laychoo, K. Kunnika and W. Prapon, *Eur. J. Pharm. Sci*., **6**, 19 (1998).

[6a] U. Eisner, and J. Kuthan, *Chem. Rev*., **72**, 1 (1972); [b] D. M. Stout and A. I. Meyers, *Chem. Rev*. **82**, 223 (1982).

[7a] R. J. Chorvat and K. J. Rorig, *J. Org. Chem*., **53**, 5779 (1988); [b] C. O. Kappe and W. M. F. Fabian, *Tetrahedron*, **53**, 2803 (1997); [c] C. O. Kappe, *Tetrahedron*, **49**, 6397 (1993).

[8] S. J. Tu, C. B. Miao, F. Fang, Y. J. Feng, T. J. Li, Q. Y. Zhuang, X. J. Zhang, S. L. Zhu and D. Q. Shi, *Bioorg. Med. Chem. Lett*., **14**, 1533 (2004).

[9a] R. D. Larsen, E. G. Corley, A. O. King, J. D. Carrol, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang and R. Zamboni, *J. Org. Chem*., **61**, 3398 (1996); [b] Y. L. Chen, K. C. Fang, J. Y. Sheu, S. L. Hsu and C. C. Tzeng, *J. Med. Chem*., **44**, 2374 (2001); [c] G. Roma, M. D. Braccio, G. Grossi and M. Chia, *Eur. J. Med. Chem*., **35**, 1021 (2000).

[10] D. Doube, M. Bloun, C. Brideau, C. Chan, S. Desmarais, D. Eithier, J. P. Falgueyeret, R. W. Friesen, M. Girad, Y. Girad, J. Guay, P. Tagari and R. N. Yong, *Bioorg. Med. Chem. Lett*., **8**, 1225 (1998).

[11a] M. P. Maguire, K. R. Sheets, K. Mcvety, A. P. Spada and A. Ziberstein, *J. Med. Chem*., **37**, 2129 (1994); [b] O. Bilker, V. Lindo, M. Panico, A. E. Etiene, T. Paxton, A. Dell, M. Rogers, R. E. Sinden and H. R. Morris, *Nature*, **392**, 289 (1998).

[12] S. Margarita, V. Yamila, O. Estael, M. Nazario, M. Roberto, Q. Margaria, S. Carlos, S. Jose L. N. Hector, B. Norbert, P. Oswald M and D. Camiel, *J. Heterocyclic Chem*., **37**, 735 (2000).

[13a] S. J. Tu, F. Fang, C. B. Miao, H. jiang, Y. J. Feng, D. Q. Shi and X. S. Wang, *Tetrahedron Lett.*, **44**, 6153 (2003); [b] S. J. Tu, T. J. Li, F. Shi, F. Fang, S. L. Zhu, X. Y. Wei and Z. M. Zong, *Chem Lett*., **34**, 733 (2005).

[14a] The crystal data for **4a**: $C_{18}H_{20}N_3O_{1.5}$, *Mr* =302.37, Monoclinic *P* 21/c, *a* =9.1652 (13) Å, *b* = 14.716(2) Å, *c* = 23.596 (3) Å, *V* = 3175.1 (7) $Å^3$, Z = 8, T = 193 (2) K , μ = 0.08 mm^{-1}, *F*(000) =1288, 35240reflections measured, 7266 unique reflections, *R* = 0.068, *wR*= 0.143; [b] S. J. Tu, J. P. Zhang, X. T. Zhu, J. N. Xu and Q. Wang, *Acta Cryst*., **E61**, o983 (2005).