An improved synthesis of reduced 9-arylacridine-1,8-diones from 3-amino-5,5-dimethylcyclohex-2-enone, arylaldehydes and 1,3-dicarbonyl compounds in aqueous medium

Xiang-Shan Wang[a,b,c]*, Mei-Mei Zhang[a], Da-Qing Shi[a,c], Shu-Jiang Tu[a,c], Xian-Yong Wei[b] and Zhi-Min Zong[b]

[a]*Department of Chemistry, Xuzhou Normal University, Xuzhou Jiangsu, 221 116, China*

[b]*School of Chemical Engineering, China University of Mining and Technology, Xuzhou Jiangsu 221 008, China*

[c]*The Key Laboratory on Biotechnology for Medical Plant of Jiangsu Province, Xuzhou 221 116, China*

An improved and green synthesis of 9-arylacridine-1,8-dione derivatives was accomplished by the reaction of 3-amino-5,5-dimethylcyclohex-2-enone, arylaldehydes and 1,3-dicarbonyl compounds in aqueous medium. Novel unsymmetrical 9-arylacridine-1,8-diones differently substituted at the 3 and 6 positions were obtained by this procedure.

Keywords: acridine-1,8-diones, aldehydes, reactions in water, PTC, TBAC

1,4-Dihydropyridine and its derivatives are well-known compounds that are widely prescribed as calcium β-blockers, and used for the treatment of hypertension and heart defibrillation.[1] There are many methods available for the synthesis of tricyclic compounds containing the 1,4-dihydropyridine residue, such as 9-arylacridines, from aldehyde, dimedone and ammonium acetate via traditional heating in organic solvents,[2] or in water catalysed by TEBAC (triethylbenzylammonium chloride),[3] or under microwave irradiation,[4] or in ionic liquids.[5]

In addition, acridines are important compounds reported to possess antitumour,[6] cytotoxic,[7] anticancer,[8] antimicrobial,[9] anti-MDR,[10] fungicidal,[11] antibacterial and fungicidal activity.[12] To the best of our knowledge, the known 9-arylacridine-1,8-diones are symmetrical, containing the same functional groups (methyl groups) at the 3 and 6 positions. In view of the emerging importance of water as a novel reaction medium, it has been considered as a very promising and attractive substitute for volatile organic solvents, and has been widely used in the Green Chemistry area, since Breslow,[13] who showed that hydrophobic effects could strongly enhance the rates of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in 1980s. There has been a growing recognition that water is an attractive medium for a large number of organic reactions,[14] being inexpensive, less dangerous and environment-friendly. As part of our current studies on the development of new routes to heterocyclic systems, we now report an efficient and clean synthetic route to symmetrical and unsymmetrical 9-arylacridine-1,8-dione derivatives in aqueous medium by the reaction of 3-amino-5,5-dimethylcyclohex-2-enone, arylaldehyde and 1,3-dicarbonyl compounds, catalysed by TEBAC.

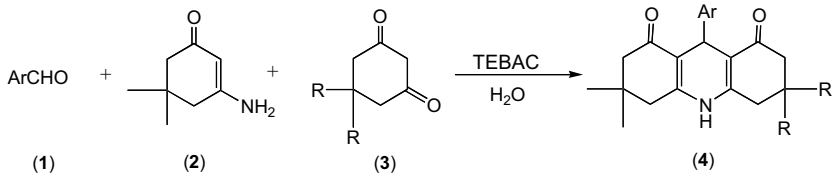
When the reactions of arylaldehydes (**1**), 3-amino-5,5-dimethylcyclohex-2-enone (**2**),[15] and 1,3-dicarbonyl compounds (**3**) were performed in water at 90°C (Scheme 1), the desired symmetrical and unsymmetrical 9-arylacridine-1,8-dione derivatives **4** were obtained successfully in high yields in a few hours.

We began our study of the reaction shown in Scheme 1 by optimising the reaction conditions for the preparation of 9-arylacridine derivative **4a**. A summary of the optimisation experiment is provided in Table 1. It turned out that at room temperature, no reaction would be carried out even when the amount of catalyst (TEBAC) was increased to 20 mol% (Table 1, entries 1 and 2). The catalyst plays a crucial role in

Table 1 Synthesis of **4a** in water under different reaction conditions[a]

Entry	Temperature/°C	Amount/ mol%	Catalyst	Time/h/%	Yield[b]
1	r.t.	10	TEBAC	3	0
2	r.t.	20	TEBAC	6	0
3	100	10	TEBAC	3	79
4	100	10	TEBAC	6	92
5	100	10	TEBAC	9	92
6	100	5	TEBAC	6	84
7	100	20	TEBAC	6	92
8	100	10	$CH_3(CH_2)_{15}NMe_3Br$	6	89
9	100	10	$CH_3(CH_2)_{11}SO_3Na$	6	90

[a]Reaction conditions: 10 ml water, 2 mmol **1a** and 2 mmol **2** and 2 mmol 5,5-dimethyl-1,3-cyclohexanedione.



Scheme 1

* Correspondent. E-mail: xswang1974@yahoo.com

the success of the reaction in terms of the rate and the yield. From Table 1, we can see using of just 10 mol% TEBAC in water at reflux is sufficient to make the reaction happen. An increase in the quantity of the catalyst does not result in any improvement of the reaction. To find the optimum reaction time, the reaction was carried out in the presence of a given amount of TEBAC (here we used 10 mol%) for 3, 6 or 9 hours, resulting in the isolation of **4a** in 79%, 92% and 92% yield respectively. Thus, 10 mol% TEBAC and a reaction time of 6 hours were chosen. Moreover, different catalysts were further studied, from Table 1 we could conclude that the TEBAC works best for this reaction catalyst for this reaction. Moreover, the catalyst solution can be reused for the synthesis of **4a** without significant loss of activity. This was established over four cycles of the reaction.

In order to demonstrate the efficiency and versatility of the present method, we performed the reaction of a variety of arylaldehydes **1, 2** and 1,3-dicarbonyl compounds **3** at 100°C in aqueous medium. As shown in Table 2, we can see a series of **1**, either the aromatic ring containing electron-withdrawing groups (such as halo or nitro) or electron-donating groups (such as alkoxy or alkyl), reacted well with **2** and **3** to give the corresponding products **4** in high yields under the same reaction conditions. We concluded that no obvious effects of electron and nature of substituents on the aromatic ring were observed. Meanwhile, from entries 11 to 17, it is seen that there are no groups on the 6-position in the 9-arylacridine-1,8-dione moieties **4k–q**, which are unsymmetrical products.

In conclusion, we have developed a novel synthetic method for the synthesis of 9-arylacridine-1,8-dione derivatives in aqueous media. Compared with other methods,[2-5] not only the symmetrical but also the unsymmetrical 9-arylacridin-1,8-diones moiety with different groups in 3 and 6 positions all gave the excellent yields. Meanwhile, the water was chosen as green solvent, which could be reused for several rounds without significant loss of activity.

Experimental

Melting points were determined in open capillaries. IR spectra were recorded on a TENSOR 27 spectrometer in KBr. ^{1}H NMR spectra were obtained for solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. Elemental analyses were carried out using Perkin-Elmer 240 analyser.

General procedure

A suspension of a mixture of arylaldehyde **1** (2 mmol), 3-amino-5,5-dimethylcyclohex-2-enone **2** (2 mmol) 1,3-dicarbonyl compounds 3 (2 mmol) and TEBAC (0.2 mmol) was stirred in water (10 ml) at 100°C for 3–8 h. The crystalline powder which was formed was collected by filtration; the filtrate containing TEBAC could be reused directly without significant loss of activity. The crude product was washed with water and recrystallised from DMF and water to give pure 9-arylacridine-1,8-dione derivatives **4**.

The data of the new compounds are as follows:

9-(3-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4a**): IR (KBr): ν_{max} 3274, 3061, 2959, 1645, 1613, 1489, 1426, 1397, 1366, 1257, 1221 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 0.86 (s, 6H, $2CH_3$), 1.01 (s, 6H, $2CH_3$), 2.00 (d, J = 16.0 Hz, 2H, 2CH), 2.19 (d, J = 16.0 Hz, 2H, 2CH), 2.34 (d, J = 17.2 Hz, 2H, 2CH), 2.46 (d, J = 17.2 Hz, 2H, 2CH), 4.78 (s, 1H, CH), 7.08–7.14 (m, 3H, ArH), 7.19–7.23 (m, 1H, ArH), 9.44 (s, 1H, NH). Anal. Calcd for $C_{23}H_{26}ClNO_2$: C 71.96, H 6.83, N 3.65; found C 71.88, H 6.90, N 3.75%.

9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4b**): IR (KBr): ν_{max} 3278, 3055, 2960, 2872, 1646, 1618, 1478, 1397, 1367, 1256, 1222 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.86 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.97 (d, J = 16.0 Hz, 2H, 2CH), 2.18 (d, J = 16.0 Hz, 2H, 2CH), 2.32 (d, J = 17.2 Hz, 2H, 2CH), 2.45 (d, J = 17.2 Hz, 2H, 2CH), 4.79 (s, 1H, CH), 6.96–7.02 (m, 2H, ArH), 7.14–7.17 (m, 2H, ArH), 9.35 (s, 1H, NH). Anal. Calcd for $C_{23}H_{26}FNO_2$: C 75.18, H 7.13, N 3.81; found C 75.03, H 7.28, N 3.80%.

9-(3,4-Dichlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4c**): IR (KBr): ν_{max} 3176, 3060, 2956, 2882, 2809, 1648, 1611, 1493, 1464, 1396, 1366, 1260, 1221 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.87 (s, 6H, $2CH_3$), 1.01 (s, 6H, $2CH_3$), 2.01 (d, J = 16.0 Hz, 2H, 2CH), 2.19 (d, J = 16.0 Hz, 2H, 2CH), 2.35 (d, J = 17.2 Hz, 2H, 2CH), 2.46 (d, J = 17.2 Hz, 2H, 2CH), 4.77 (s, 1H, CH), 7.11 (dd, J = 8.0 Hz, J' = 1.6 Hz, 1H, ArH), 7.31 (d, J = 1.6 Hz, ArH), 7.46 (d, J = 8.0 Hz, ArH), 9.45 (s, 1H, NH). Anal. Calcd for $C_{23}H_{25}Cl_2NO_2$: C 66.03, H 6.02, N 3.35; found C 65.90, H 6.15, N 3.42%.

9-(3-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4d**): IR (KBr): ν_{max} 3284, 3210, 3072, 2960, 2871, 1650, 1622, 1588, 1482, 1398, 1369, 1264, 1224 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.88 (s, 6H, $2CH_3$), 1.01 (s, 6H, $2CH_3$), 1.99 (d, J = 16.0 Hz, 2H, 2CH), 2.17 (d, J = 16.0 Hz, 2H, 2CH), 2.31 (d, J = 16.8 Hz, 2H, 2CH), 2.44 (d, J = 16.8 Hz, 2H, 2CH), 4.73 (s, 1H, CH), 6.42 (dd, J = 8.0 Hz, J' = 2.0 Hz, 1H, ArH), 6.56 (d, J = 8.0 Hz, ArH), 6.62 (s, 1H, ArH), 6.94–6.90 (m, 1H, ArH), 9.08 (s, 1H, NH), 9.28 (s, 1H, OH). Anal. Calcd for $C_{23}H_{27}NO_3$: C 75.59, H 7.45, N 3.83; found C 75.50, H 7.60, N 3.97%.

9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4e**): IR (KBr): ν_{max} 3277, 3200, 2954, 2932, 2873, 1641, 1614, 1589, 1510, 1475, 1422, 1398, 1373, 1263, 1221 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.87 (s, 6H, $2CH_3$), 1.01 (s, 6H, $2CH_3$), 1.98 (d, J = 16.0 Hz, 2H, 2CH), 2.16 (d, J = 16.0 Hz, 2H, 2CH), 2.30 (d, J = 16.8 Hz, 2H, 2CH), 2.48 (d, J = 16.8 Hz, 2H, 2CH), 4.70 (s, 1H, CH), 6.52 (d, J = 8.4 Hz, 2H, ArH), 6.92 (d, J = 8.4 Hz, 2H, ArH), 9.04 (s, 1H, NH), 9.23 (s, 1H, OH). Anal. Calcd for $C_{23}H_{27}NO_3$: C 75.59, H 7.45, N 3.83; found C 75.54, H 7.58, N 3.92%.

3,3,6,6-Tetramethyl-9-(2-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4f**): IR (KBr): ν_{max} 3280, 3074, 2957, 2871, 1635, 1577, 1530, 1489, 1424, 1397, 1365, 1298, 1257, 1225 cm^{-1}.

Table 2 Synthesis of **4** in water[a]

Entry	Ar	R	Time/h	Product	Yields/%	M.p./°C(Lit.)
1	3-ClC_6H_4	CH_3	6	**4a**	93	295–297 (-)
2	4-FC_6H_4	CH_3	5	**4b**	96	252–253 (-)
3	3,4-$Cl_2C_6H_3$	CH_3	4	**4c**	95	> 300 (-)
4	3-OHC_6H_4	CH_3	6	**4d**	98	> 300 (-)
5	4-OHC_6H_4	CH_3	6	**4e**	92	> 300 (-)
6	2-$NO_2C_6H_4$	CH_3	3	**4f**	90	> 300 (-)
7	4-ClC_6H_4	CH_3	5	**4g**	92	298–301 (296–298)[5]
8	4-$CH_3OC_6H_4$	CH_3	7	**4h**	93	274–275 (273–275)[5]
9	4-$N(CH_3)_2C_6H_4$	CH_3	8	**4i**	90	272–273 (270–272)[5]
10	3,4-$(CH_3O)_2C_6H_3$	CH_3	8	**4j**	93	261–262 (261–262)[5]
11	4-OHC_6H_4	H	6	**4k**	90	284–285 (-)
12	C_6H_5	H	6	**4l**	95	260–262 (-)
13	3,4-$(CH_3)_2C_6H_3$	H	6	**4m**	96	280–282 (-)
14	4-$CH_3OC_6H_4$	H	6	**4n**	95	270–272 (-)
15	3-ClC_6H_4	H	5	**4o**	98	260–262 (-)
16	4-ClC_6H_4	H	5	**4p**	92	> 300 (-)
17	2,4-$Cl_2C_6H_3$	H	4	**4q**	92	268–270 (-)

[a]Reaction conditions: 10 ml water, 2 mmol **1** and 2 mmol **2** and 2 mmol **3**. [b]Isolated yields.

^{1}H NMR (DMSO-d_6): δ 0.85 (s, 6H, 2CH$_3$), 1.00 (s, 6H, 2CH$_3$), 1.92 (d, *J* = 16.0 Hz, 2H, 2CH), 2.15 (d, *J* = 16.0 Hz, 2H, 2CH), 2.32 (d, *J* = 17.2 Hz, 2H, 2CH), 2.45 (d, *J* = 17.2 Hz, 2H, 2CH), 5.61 (s, 1H, CH), 7.25–7.29 (m, 1H, ArH), 7.33 (d, *J* = 8.0 Hz, 1H, ArH), 7.51–7.55 (m, 1H, ArH), 7.72 (d, *J* = 8.0 Hz, 1H, ArH), 7.19–7.23 (m, 1H, ArH), 9.37 (s, 1H, NH). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C 70.03, H 6.64, N 7.10; found C 69.94, H 6.78, N 7.11%.

(±)-9-(4-Hydroxyphenyl)-3,3-dimethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4k**): IR (KBr): ν_{max} 3299, 3090, 2952, 1620, 1589, 1510, 1470, 1396, 1367, 1257, 1229 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.88 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 1.74–1.79 (m, 1H, CH), 1.88–1.94 (m, 1H, CH), 1.99 (d, *J* = 16.0 Hz, 1H, CH), 2.14–2.22 (m, 3H, 3CH), 2.30 (d, *J* = 17.2 Hz, 1H, CH), 2.42 (d, *J* = 17.2 Hz, 1H, CH), 2.48–2.52 (m, 3H, 3CH), 4.75 (s, 1H, CH), 6.53 (d, *J* = 8.4 Hz, 2H, ArH), 6.93 (d, *J* = 8.4 Hz, 2H, ArH), 9.02 (s, 1H, NH), 9.29 (s, 1H, OH). Anal. Calcd for $C_{21}H_{23}NO_3$: C 74.75, H 6.87, N 4.15; found C 74.68, H 6.95, N 4.20%.

(±)-3,3-Dimethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4l**): IR (KBr): ν_{max} 3300, 3060, 2951, 2872, 1644, 1621, 1598, 1478, 1429, 1392, 1364, 1334, 1232 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.87 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 1.76–1.82 (m, 1H, CH), 1.89–1.96 (m, 1H, CH), 2.00 (d, *J* = 16.0 Hz, 1H, CH), 2.15–2.22 (m, 3H, 3CH), 2.33 (d, *J* = 17.2 Hz, 1H, CH), 2.44 (d, *J* = 17.2 Hz, 1H, CH), 2.48–2.52 (m, 3H, 3CH), 4.86 (s, 1H, CH), 7.02–7.06 (m, 1H, ArH), 7.15–7.18 (m, 5H, ArH), 9.37 (s, 1H, NH). Anal. Calcd for $C_{21}H_{23}NO_2$: C 78.47, H 7.21, N 4.36; found C 78.40, H 7.32, N 4.44%.

(±)-9-(3,4-Dimethylphenyl)-3,3-dimethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4m**): IR (KBr): ν_{max} 3297, 3067, 2950, 1644, 1609, 1478, 1393, 1361, 1231 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.88 (s, 3H, CH$_3$), 1.00 (s, 3H, CH$_3$), 1.75–1.80 (m, 1H, CH), 1.89–1.95 (m, 1H, CH), 1.98 (d, *J* = 16.0 Hz, 1H, CH), 2.08 (s, 3H, CH$_3$), 2.10 (s, 3H, CH$_3$), 2.14–2.18 (m, 3H, 3CH), 2.32 (d, *J* = 17.2 Hz, 1H, CH), 2.43 (d, *J* = 17.2 Hz, 1H, CH), 2.48–2.51 (m, 3H, 3CH), 4.75 (s, 1H, CH), 6.81–6.90 (m, 4H, ArH), 9.34 (s, 1H, NH). Anal. Calcd for $C_{23}H_{27}NO_2$: C 79.05, H 7.79, N 4.01; found C 78.89, H 7.86, N 4.11%.

(±)-9-(4-Methoxyphenyl)-3,3-dimethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4n**): IR (KBr): ν_{max} 3290, 3058, 3010, 2950, 2868, 2829, 1642, 1610, 1509, 1477, 1393, 1364, 1299, 1264, 1233 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.87 (s, 3H, CH$_3$), 1.00 (s, 3H, CH$_3$), 1.74–1.81 (m, 1H, CH), 1.90–1.96 (m, 1H, CH), 1.99 (d, *J* = 16.0 Hz, 1H, CH), 2.14–2.22 (m, 3H, 3CH), 2.31 (d, *J* = 17.2 Hz, 1H, CH), 2.47 (d, *J* = 17.2 Hz, 1H, CH), 2.49–2.51 (m, 3H, 3CH), 3.65 (s, 3H, CH$_3$O), 4.78 (s, 1H, CH), 6.71 (d, *J* = 8.4 Hz, 2H, ArH), 7.04 (d, *J* = 8.4 Hz, 2H, ArH), 9.37 (s, 1H, NH). Anal. Calcd for $C_{22}H_{25}NO_3$: C 75.19, H 7.17, N 3.99; found C 75.05, H 7.21, N 3.99%.

(±)-9-(3-Chlorophenyl)-3,3-dimethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4o**): IR (KBr): ν_{max} 3286, 3067, 2958, 2871, 1645, 1605, 1478, 1428, 1394, 1363, 1338, 1234 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.87 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 1.73-1.83 (m, 1H, CH), 1.88–1.94 (m, 1H, CH), 2.01 (d, *J* = 16.0 Hz, 1H, CH), 2.16–2.24 (m, 3H, 3CH), 2.35 (d, *J* = 17.2 Hz, 1H, CH), 2.46 (d, *J* = 17.2 Hz, 1H, CH), 2.49–2.52 (n, 3H, 3CH), 4.82 (s, 1H, CH), 7.11–7.14 (m, 3H, ArH), 7.19–7.23 (m. 1H, ArH), 9.50 (s, 1H, NH). Anal. Calcd for $C_{21}H_{22}ClNO_2$: C 70.88, H 6.23, N 3.94; found C 70.69, H 6.35, N 3.97%.

(±)-9-(4-Chlorophenyl)-3,3-dimethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4p**): IR (KBr): ν_{max} 3277, 3062, 2954, 1642, 1610, 1488, 1394, 1366, 1261, 1226 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.86 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 1.75–1.81 (m, 1H, CH), 1.87–1.94 (m, 1H, CH), 1.99 (d, *J* = 16.0 Hz, 1H, CH), 2.15–2.22 (m, 3H, 3CH), 2.33 (d, *J* = 17.2 Hz, 1H, CH), 2.44 (d, *J* = 17.2 Hz, 1H, CH), 2.48–2.53 (m, 3H, 3CH), 4.83 (s, 1H, CH), 7.15 (d, *J* = 8.4 Hz, 2H, ArH), 7.22 (d, *J* = 8.4 Hz, 2H, ArH), 9.43 (s, 1H, NH). Anal. Calcd for $C_{21}H_{22}ClNO_2$: C 70.88, H 6.23, N 3.94; found C 70.77, H 6.36, N 3.95%.

(±)-9-(3,4-Dichlorophenyl)-3,3-dimethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4q**): IR (KBr): ν_{max} 3270, 3066, 2953, 1647, 1616, 1483, 1422, 1393, 1366, 1261, 1231 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.87 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 1.71–1.76 (m, 1H, CH), 1.86–1.89 (m, 1H, CH), 1.93 (d, *J* = 16.4 Hz, 1H, CH), 2.09–2.19 (m, 3H, 3CH), 2.28 (d, *J* = 17.2 Hz, 1H, CH), 2.42–2.50 (m, 4H, 4CH), 5.05 (s, 1H, CH), 7.23–7.31 (m, 3H, ArH), 9.46 (s, 1H, NH). Anal. Calcd for $C_{21}H_{21}Cl_2NO_2$: C 64.62, H 5.42, N 3.59; found C 64.60, H 5.53, N 3.57%.

Received 16 July 2006; accepted 26 September 2006
Paper 06/4087

References

1 R.A. Janis, P.J. Silver and D.J. Triggle, *Adv. Drug. Res*. 1987, **16**, 309; (b) R. Shan, C. Velazquez and E.E. Knaus, *J. Med. Chem*. 2004, **41**, 254; (c) A.F. Dulhunty, S.M. Curtis, S. Watson, L. Cengia and G. Marco, *J. Biol. Chem.* 2004, **279**, 11853.
2 N. Martin, M. Quinteiro, C. Seoane, L. Mora, M. Suarez, E. Ochoa and A. Morales, *J. Heterocycl. Chem*. 1995, **51**, 235.
3 X.S. Wang, M.M. Zhang, Z.S. Zeng, D.Q. Shi, S.J. Tu, X.Y. Wei and Z.M. Zong, *Tetrahedron Lett*. 2005, **46**, 7169; (b). X.S. Wang, D.Q. Shi, Y.F. Zhang, S.H. Wang and S.J. Tu, *Chin. J. Org. Chem.* 2004, **24**, 430.
4 S.J. Tu, C.B. Miao, Y. Gao, Y.J. Feng and J.C. Feng, *Chin. J. Chem*. 2002, **20**, 703.
5 Y.L. Li, M.M. Zhang, X.S. Wang, D.Q. Shi, S.J. Tu, X.Y. Wei and Z.M. Zong, *J. Chem. Res.* 2005, 600.
6 Y. Mikata, M. Yokoyama, K. Mogami, M. Kato, I. Okura, M. Chikira and S. Yano, *Inorg. Chim. Acta*, 1998, **279**, 51.
7 Antonini, P. Polucci, L.R. Kelland, E. Menta, N. Pescalli and S. Martelli, *J. Med. Chem.*, 1999, **42**, 2535.
8 S.A. Gamage, J.A. Spicer, G.J. Atwell, G.J. Finlay, B.C. Baguley and W.A. Denny, *J. Med. Chem.* 1999, **42**, 2383.
9 N.M. Eid, H.M. Safwat, M.A. Ramadan, S.A. Shouman and A.A. El-Esawy, *Bull. Fac. Pharm.* 1995, **33**, 25.
10 S. Gallo, S. Atifi, A. Mahamoud, C. Santelli-Rouvier, K.M.J. Wolfart and J. Barbe, *Eur. J. Med. Chem.* 2003, **38**, 19.
11 Srivastava and C. Nizamuddin, *Indian J. Heterocycl. Chem*. 2004, **13**, 261.
12 L. Ferencz and M. Peter, *Farmacia* 2003, **51**, 52.
13 R. Breslow and D.C. Rideout, *J. Am. Chem. Soc.* 1980, **102**, 7816; (b) R. Breslow, *Acc. Chem. Res.* 1991, **24**, 159.
14 A.A. Ponaras, *J. Org. Chem*. 1983, **48**, 3866; (b) R.M. Coates, B.D. Rogers, S.J. Hobbs, D.R. Peck and D.P. Curran, *J. Am. Chem. Soc*. 1987, **109**, 1160; (c) H. Mattes and C. Benezra, *Tetrahedron Lett*. 1985, **26**, 5697; (d) J.Y. Zhou, G.D. Lu and S.H. Wu, *Synth. Commun*. 1992, **22**, 481; (e) P. Delair and J. L. Luche, *J. Chem. Soc., Chem. Commun*. 1989, 398; (f) X.S. Wang, M.M. Zhang, Z.S. Zeng, D.Q. Shi, S.J. Tu, X.Y. Wei and Z.M. Zong, *Chem. Lett.* 2005, **34**, 1316; (g) X.S. Wang, Z.S. Zeng, M.M Zhang, Y.L. Li, D.Q. Shi, S.J. Tu, X.Y. Wei and Z.M. Zong, *J. Chem. Res.* 2006, 228.
15 P.G. Baraldi, D. Simoni and S. Manfredini, *Synthesis*, 1980, 902.