One-pot Synthesis of a Novel Compound *N*-Hydroxydeca-hydroacridine under Microwave Irradiation

Shujiang Tu,* Fang Fang, Songlei Zhu, Tuanjie Li, Xiaojing Zhang, Qiya Zhuang

Department of Chemistry, Xuzhou Normal University, Key Laboratory of Biotechnology on Medical Plant, Xuzhou; Jiangsu, 221009, P. R. China
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A novel reaction to synthesis a series new *N*-hydroxyldecahydroacridine derivatives by a one-pot condensation of aldehyde, 1,3-dicarbonyl compound and NH_2OH in glycol under microwave irradiation is described. *N*-hydroxyldecahydroacridine was obtained in excellent yields (81-95%) within short reaction time (4-7 min)

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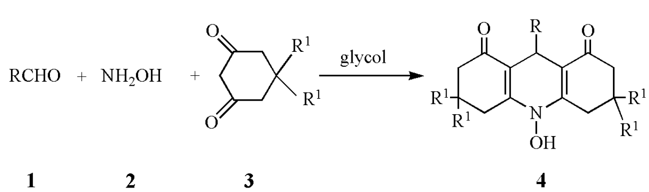
1,4-Dihydropyridines (1,4-DHPs), an important class of compounds, have exhibited important pharmacological properties, *e.g.* as calcium channel modulators [1], and in the treatment of cardiovascular disorder [2]. The chemical modifications of the DHP ring such as the introduction of different substituents [3] or heteroatoms [4] have allowed expansion of research on the structure-activity relationship to afford new insight into molecular interactions at the receptor level. In fact, it is well established that slight structural modifications on the DHP ring may bring various pharmacological effects [5]. In our previous paper, we disclosed the modification of 1,4-DHPs fused with one [6] or two [7] cyclohexanone rings and obtained the 1,4-Dihydropyridines derivatives, such as decahydroacridine.

Suárez *et al* reported the synthesis of decahydroacridine [8]. In order to look for some new compounds with interesting biological properties, we would like to introduce a hydroxyl on the nitrogen of decahydroacridine to modify the decahydroacridine ring.

In our previous paper, we have reported the method of producing *N*-hydroxydecahydroacridine by the reaction of aldoxime and dimedone. However the aldoxime must be prepared from aldehyde and NH_2OH [9]. In connection with our previous studies, to modify 1,4-dihydropyridines, we described here a facile one-pot condensation of aldehyde, cyclic 1,3-dicarbonyl compounds and NH_2OH in glycol under the irradiation of microwave to afford a new type of heterocyclic compounds, the N-hydroxydecahydroacridine derivatives (Scheme 1).

The application of microwave irradiation as a non-conventional energy source for activation of reactions, has now gained extensive usage, as it leads to enhance reaction rates, higher yields of pure products, easier work-up, and sometimes, to selective conversions.

Scheme 1

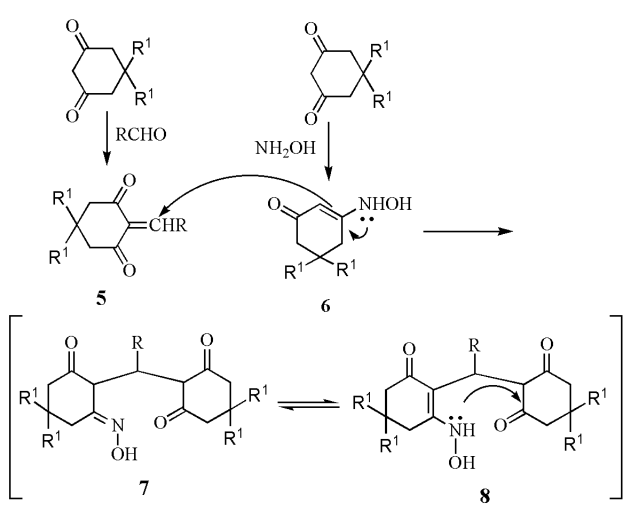


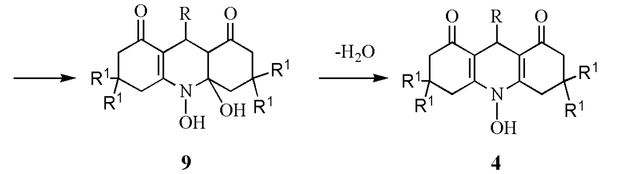
1 2 3 4

This reaction may occur *via* an condensation, addition, cyclization, elimination mechanism (Scheme 2). The condensation between aldehyde and dimedone gave 2-aryllidene-5,5-dimethyl-1,3-cyclo-hexanedione **5**. Michael addition between **5** and **6** (obtained from dimedone and NH_2OH) then furnished the intermediate **7**, which isomerized to **8**. Intramolecular cyclodehydration of **9** gave **4**.

The results (Table 1) show a series of aldehydes that undergo the cyclocondensation to give excellent yields (81-95%) of the products. The procedure is simple to operate, and the work-up consists of simple filtration. All the products were characterized by IR, ^{1}H NMR analysis. And the elemental analyses of these compounds are in agreement with their structures. Furthermore, the structure of **4a**

Scheme 2





9 4

and **4i** was established by an X-ray crystallographic analysis [10] (Figures 1 and 2).

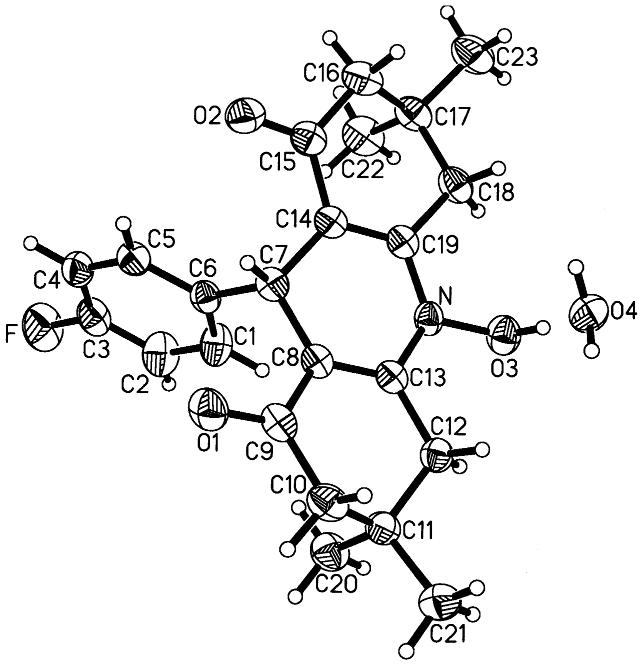


Figure 1. ORTEP diagram of **4a**.

synthesis of *N*-hydroxydecahydroacridine derivatives therefore is a simple, timesaving high-yielding, and environmentally friendly process. Efforts are underway to elaborate these to biologically active heterocycles and these results will be reported in due course.

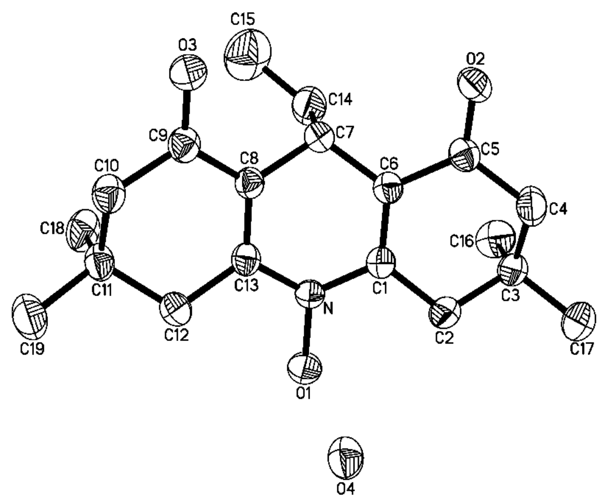


Figure 2. ORTEP diagram of **4i**.

Table 1

Synthesis of **4** Under Microwave Irradiation

Entry	R	R^1	Time (min)	Yield (%)	Mp (°C)
4a	$4\text{-}FC_6H_4$	CH_3	5 [a] (85 [b])	90 [a] (80 [b])	233-234
4b	$2\text{-}ClC_6H_4$	CH_3	6 [a] (100 [b])	88 [a] (76 [b])	222-223
4c	$4\text{-}ClC_6H_4$	CH_3	5 [a] (75 [b])	92 [a] (84 [b])	256-257
4d	$3,4\text{-}OCH_2OC_6H_3$	CH_3	4 [a]	93	248-249
4e	$3\text{-}NO_2C_6H_4$	CH_3	6 [a]	92	136-137
4f	$4\text{-}NO_2C_6H_4$	CH_3	5 [a]	95	134-135
4g	$4\text{-}N(CH_3)_2C_6H_3$	CH_3	7 [a]	88	159-160
4h	2-Furan	CH_3	6 [a]	83	196-197
4i	CH_3CH_2	CH_3	5 [a]	81	204-205
4j	$CH_3CH_2CH_2$	CH_3	5 [a]	85	152-153
4k	$4\text{-}ClC_6H_4$	H	5 [a]	92	>300
4l	$4\text{-}OCH_3C_6H_4$	H	7 [a]	89	>300
4m	$2,4\text{-}Cl_2C_6H_3$	H	7 [a]	92	>300
4n	$3,4\text{-}Cl_2C_6H_3$	H	7 [a]	89	247-248

[a] Method A: in glycol, under microwave irradiation; [b] Method B: in glycol at 110 °C.

In conclusion, we have disclosed a novel microwave-assisted reaction between aldehyde and 1,3-dicarbonyl compounds, and realized the introduction of the hydroxyl on the nitrogen of acridine derivatives. Moreover, the reaction time assisted by microwave irradiation is dramatically shorter than that of the conventional heating. This one-pot

EXPERIMENTAL

Microwave irradiation was carried out in a commercial microwave oven (2450 MHz) under atmospheric pressure. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Shimadzu spectrometer. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as internal standard, DMSO-d_6 as solvent. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer.

General Procedure for Preparation of *N*-Hydroxydecahydro-acridine **4**.

The mixture of substituted aldehyde (2 mmol), 1,3-dicarbonyl compounds (4 mmol), and NH_2OH (2 mmol) in glycol (5 ml) was irradiated for 4-7 min. The reaction mixture was cooled to room temperature and poured into 50 mL of water, collection by filtration gave the crude product, which was further purified by recrystallization from 95% ethanol. All products are characterized by IR and ^{1}H NMR spectral data.

3,3,6,6-tetramethyl-*N*-hydroxy-9-(4-fluorophenyl)-1,8-dioxo-1,2, 3,4,5,6,7,8,9,10-decahydroacridine (**4a**).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3300, 2958, 2872, 2733, 2360, 1614, 1526, 1466, 1392, 1368, 1323, 1294, 1261, 1221, 1124, 1095, 1003, 851, 682, 661, 615, 569, 525, 428; ^{1}H NMR (ppm): δ 10.79(s, 1H, OH), 7.00-7.05 (m, 4H, ArH), 4.94 (s, 1H, CH), 2.07-2.62 (m, 8H, CH_2), 1.03 (s, 6H, CH_3), 0.88(6H, s, CH_3).

Anal. Calcd. for $C_{23}H_{26}FNO_3$: C, 72.04; H, 6.83; N, 3.65. Found: C, 72.31; H, 6.54; N, 3.43.

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

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3300, 2961, 2878, 2674, 1603, 1568, 1490, 1409, 1371, 1323, 1272, 1225, 1141, 1023, 902, 848, 565, 523; ^{1}H NMR (ppm): δ 10.79(s, 1H, OH), 7.13-7.26 (m, 4H, ArH), 4.93 (s, 1H, CH), 2.02-2.68 (m, 8H, CH_2), 1.04 (s, 6H, CH_3), 0.87 (s, 6H, CH_3).

Anal. Calcd. for $C_{23}H_{26}ClNO_3$: C, 69.08; H, 6.55; N, 3.50. Found: C, 69.21; H, 6.48; N, 3.72.

3,3,6,6-Tetramethyl-*N*-hydroxy-9-(4-chlorophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (**4c**).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3344, 3051, 2956, 2931, 2870, 2735, 1714, 1612, 1566, 1466, 1363, 1224, 1146, 1122, 1038, 947, 802, 746, 656, 569. ^{1}H NMR (ppm): δ 10.78 (s, 1H, OH), 7.25 (d, 2H, *J*=8.4 Hz, ArH), 7.14 (d, 2H, *J*=8.4 Hz, ArH), 5.17 (s, 1H, CH), 1.92-2.66 (m, 8H, CH_2), 1.03 (s, 6H, CH_3), 0.85 (s, 6H, CH_3).

Anal. Calcd for $C_{23}H_{26}ClNO_3$: C, 69.08; H, 6.55; N, 3.50. Found: C, 69.25; H, 6.42; N, 3.82.

3,3,6,6-Tetramethyl-*N*-hydroxy-9-(3,4-methylenedioxylphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine(**4d**).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3091, 2960, 2873, 1647, 1550, 1497, 1434, 1372, 1318, 1216, 1174, 1140, 1036, 925, 760, 569; ^{1}H NMR (ppm): δ 10.75 (s, 1H, OH), 6.60-6.73 (m, 3H, ArH), 4.88 (s, 1H, CH), 5.91 (s, 2H, CH_2), 2.03-2.68 (m, 8H, CH_2), 1.04 (s, 6H, 2CH_3), 0.89 (s, 6H, CH_3).

Anal. Calcd. for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.21; H, 6.78; N, 3.62.

3,3,6,6-Tetramethyl-*N*-hydroxy-9-(3-nitrophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (**4e**).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3153, 2956, 2873, 1649, 1606, 1558, 1529, 1470, 1358, 1325, 1260, 1223, 1176, 1142, 1124, 999, 906, 810, 733, 710, 687, 569. ^{1}H NMR (ppm): δ 10.89 (s, 1H, OH), 7.52-7.99 (m, 4H, ArH), 5.07 (s, 1H, CH), 2.04-2.71 (m, 8H, CH_2), 1.05 (s, 6H, CH_3), 0.88 (s, 6H, CH_3).

Anal. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.18; H, 6.48; N, 6.93.

3,3,6,6-Tetramethyl-*N*-hydroxy-9-(4-nitrophenyl)-1,8-dioxo-1,2,3, 4,5,6,7,8,9,10-decahydroacridine (**4f**).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3210, 2958, 2872, 1606, 1560, 1527, 1470, 1347, 1325, 1255, 1176, 1143, 1124, 1003, 899, 818, 735, 692, 569; ^{1}H NMR (ppm): δ 10.79 (s, 1H, OH), 7.15 (d, 2H, *J*=8.7 Hz, ArH), 7.24 (d, 2H, *J*=8.7 Hz, ArH), 4.93 (s, 1H, CH), 2.02-2.68 (m, 8H, CH_2), 1.04 (s, 6H, CH_3), 0.87 (s, 6H, CH_3).

Anal. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82: Found C, 67.23; H, 6.48; N, 6.98.

3,3,6,6-Tetramethyl-*N*-hydroxy-9-(4-dimethylaminophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (**4g**).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3257, 2958, 2863, 2788, 1606, 1520, 1368, 1225, 1141, 954, 832, 573. ^{1}H NMR (ppm): δ 10.76 (s, 1H, OH), 6.94 (d, 2H, *J*=8.6 Hz, ArH), 6.52 (d, 2H, *J*=8.6 Hz, ArH), 4.84 (s, 1H, CH), 2.80 (s, 6H, CH_3), 2.00-2.66 (m, 8H, CH_2), 1.04 (s, 6H, CH_3), 0.89 (s, 6H, CH_3).

Anal. Calcd. for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.90; N, 6.86. Found C, 73.28; H, 7.84; N, 6.93.

3,3,6,6-Tetramethyl-*N*-hydroxy-9-(2-furanphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (**4h**).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3308, 2958, 2930, 2867, 2728, 1605, 1562, 1501, 1469, 1359, 1324, 1262, 1220, 1142, 1072, 1007, 1072, 979, 951, 921, 884, 781, 727, 683, 616, 600, 566; ^{1}H NMR (ppm): δ 10.85 (s, 1H, OH), 7.35 (d, 1H, *J*=0.81 Hz, CH), 6.25 (dd, 1H, *J*=3.0 Hz, CH), 5.84 (d, 1H, *J*=3.3 Hz, CH), 5.12 (s, 1H, CH), 2.07-2.61 (m, 8H, CH_2), 1.05 (s, 6H, CH_3), 0.94 (s, 6H, CH_3).

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.59; H, 7.31; N, 4.16.

3,3,6,6-Tetramethyl-*N*-hydroxy-9-ethyl-1,8-dioxo-1,2,3,4,5, 6,7,8,9,10-decahydroacridine(4i).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3298, 2962, 2958, 2966, 2657, 1627, 1552, 1464, 1389, 1298, 1233, 1172, 1144, 1074, 1002, 934, 905, 887, 778, 740, 685, 612,3, 567; ^{1}H NMR (ppm): δ 10.60 (s, 1H, OH), 3.85(t, 1H, *J*=5.25 Hz, CH), 2.06-2.63 (m, 8H, CH_2), 1.16-1.20 (m, 2H, CH_2), 1.05 (s, 6H, CH_3), 1.02 (s, 6H, CH_3), 0.66 (t, 3H, *J*=7.50 Hz, CH_3).

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.01; H, 8.45; N, 4.48.

3,3,6,6-Tetramethyl-*N*-hydroxy-9-propalyl-1,8-dioxo-1,2,3,4,5, 6,7,8,9,10-decahydroacridine(**4j**).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3269, 2962, 2932, 2871, 2682, 1616, 1560, 1464, 1424, 1386, 1350, 1293, 1237, 1220, 1168, 1139, 1053, 1002, 885, 732, 686, 613, 605, 566; ^{1}H NMR (ppm): δ 10.60 (1H, s, OH), 3.87 (1H, t, *J*=5.25 Hz, CH), 2.06-2.63 (8H, m, CH_2), 1.07-1.15 (4H, m, CH_2), 1.05 (6H, s, CH_3), 1.01 (6H, s, CH_3), 0.77 (3H, t, *J*=7.30 Hz, CH_3,).

Anal. Calcd. for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.21; H, 8.95; N, 4.36.

N-Hydroxy-9-(4-chlorophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine(4k).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3313, 3221, 3078, 3043, 2950, 2883, 1664, 1639, 1470, 1357, 1168, 1127; ^{1}H NMR (ppm): δ 9.48(s, 1H, OH), 7.26(d, 2H, *J*=8.4 Hz, ArH), 7.17(d, 2H, *J*=8.4 Hz, ArH), 4.89 (s, 1H, CH), 1.83-2.35 (m, 12H, CH_2).

Anal. Calcd. for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.28; H, 5.48; N, 4.25.

N-Hydroxy-9-(4-methoxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (**4l**).

This compound was obtained according to the general method; IR (KBr, ν, cm^{-1}): 3277, 3185, 3052, 2945, 1644, 1603, 1490, 1362, 1229, 1173, 1127; ^{1}H NMR (ppm): δ 9.37(s, 1H, OH), 6.74(d, 2H, *J*=8.5 Hz, ArH), 7.07(d, 2H, *J*=8.5 Hz, ArH), 4.85 (s, 1H, CH), 1.76-2.53 (m, 12H, CH_2).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.58; H, 6.45; N, 4.29.

N-Hydroxy-9-(2,4-dichlorophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine(**4m**).

This compound was obtained according to the general method; IR (KBr, ν, cm-1): 3272, 3196, 3062, 2939, 1649, 1603, 1490, 1367, 1234, 1178, 1137; ^{1}H NMR (ppm): δ 9.51 (s, 1H, OH), 7.11-7.26 (m, 3H, ArH), 5.05 (s, 1H, CH), 1.88-2.48 (m, 12H, CH_2).

Anal. Calcd for $C_{19}H_{17}Cl_2NO_3$: C, 60.33; H, 4.53; N, 3.70. Found: C, 60.61; H, 4.18; N, 3.63.

N-Hydroxy-9-(3,4-dichlorophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (**4n**).

This compound was obtained according to the general method; IR (KBr, ν, cm-1): 3313, 3083, 3047, 2945, 1664, 1465, 1357, 1173, 1132; ^{1}H NMR (ppm): δ 9.41 (s, 1H, OH), 7.21-7.38 (m, 3H, ArH), 4.95 (s, 1H, CH), 1.96-2.54 (m, 12H, CH_2).

Anal. Calcd. for $C19H_{17}Cl_2NO_3$: C, 60.33; H, 4.53; N, 3.70. Found: C, 60.65; H, 4.21; N, 3.53.

Acknowledgments.

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[10] The sing-crystal growth was carried out in ethanol at room temperature. X-ray crystallographicanalysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer (graphite monochromator, MoKa radiation λ=0.71073 Å). The crystal crystallizes with one water molecule. Crystal data for **4a**: $C_{23}H_{28}ClFNO_4$, yellow, crystal dimension 0.58x0.58x0.40 mm, monoclinic, space group P2(1)/c, *a*=12.638(2), *b*=14.039(3), *c*=11.102(2)Å, □ =94.60(1)°, *V*=2140.2(6)Å^3, *M*r=401.46, *Z*=4, *Dc*=1.246g/cm^3, λ=0.71073Å, μ(Mok*α*)=0.09mm^{-1}, *F*(000)=856, *S*=0.906, R_1=0.0398, wR_2=0.0932. Crystal data for **4i**: $C_{19}H_{29}NO_4$, yellow, crystal dimension 0.58x0.58x0.40 mm, monoclinic, space group P2(1)/c, *a*=12.533(1), *b*=13.184(2), *c*=11.883(2) Å, □ =90°, □ =109.06(1)°, □ =90°, *V*=1856.0(5) Å^3, *Mr*=335.43, *Z*=4, *Dc*=1.201 g/cm^3, λ=0.71073 Å, μ(Mok*α*)=0.083 mm^{-1}, *F*(000)=728, *S*=1.086, R_1=0.0488, wR_2=0.1456.