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A simple and clean procedure for the synthesis of polyhydroacridine and quinoline derivatives: reaction of Schiff base with 1,3-dicarbonyl compounds in aqueous medium

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Abstract—A clean and simple synthesis of benzo[*c*]acridine, benzo[*a*]acridine, pyrido[2,3-*c*]acridine and benzo[*f*]quinoline derivatives was accomplished in good to excellent yields via the reaction of Schiff base with 1,3-dicarbonyl compounds in aqueous medium catalyzed by TEBA. The structures were characterized by ^{1}H NMR, IR and elemental analysis, and confirmed by X-ray diffraction study.

Since Breslow demonstrated hydrophobic effects could strongly enhance the rate of some organic reactions and rediscovered the use of water as solvent in organic chemistry in 1980s,[1] there has been a growing recognition that water has become an attractive medium for many organic reactions, such as Diels–Alder reactions,[2] Claisen rearrangement reactions,[3] Reformatsky reactions[4] and Pinacol-coupling reactions,[5] not only for the advantages concerning the avoidance of expensive drying reactants, catalysts and solvents, but also for some unique reactivity and selectivity.[6,7] On the other hand, organic reactions in water without using harmful organic solvents is one of the current focuses today especially in the environmentally conscious society, because water is abundant, nontoxic and environment-friendly when compared with organic solvents used accordingly.

1,4-Dihydropyridines (1,4-DHPS) are well-known compounds for their pharmacological profile in calcium channel modulations.[8] The chemical modifications on the DHP ring, such as different substituents[9] or heteroatoms,[10] have allowed the study of the extended structure and activity relationship and also provided some insight into the molecular interactions at the receptor level. The general method for the synthesis of 1,4-DHPS is from the reaction of meldrum's acid and dimedone in the presence of different aldehydes catalyzed by ammonium acetate.[11] Recently, there are many other methods available for the construction of tricycle compounds containing the 1,4-dihydropyridines, for instance acridine derivatives, by heating appropriate aldehyde, dimedone and ammonium acetate in conventional organic solvents[12] or under microwave irradiation.[13] As a consequence of our interest in the aqueous-medium organic syntheses,[14] herein, we would like to report a highly efficient method for the synthesis of a series of polyhydroacridine derivatives and quinoline derivatives via the reaction of Schiff base and 1,3-dicarbonyl compounds in water catalyzed by TEBA (benzyltriethylammonium chloride).

When the reaction of *N*-arylidenenaphthalen-1-amine or *N*-arylidenequinolin-5-amine **1** and dimedone **2** was performed in water in the presence of TEBA at 100 °C, 3,3-dimethyl-9-aryl-1,2,3,4,9,10-hexahydrobenzo[*c*]acridine-1-one derivatives or 3,3-dimethyl-9-aryl-1,2,3,4,9,10-hexahydropyrido[2,3-*c*]acridine-1-one derivatives **3** were obtained in high yields (Scheme 1). The results are summarized in Table 1.

Keywords: Acridine; Quinoline; Schiff base; Aqueous medium; TEBA.
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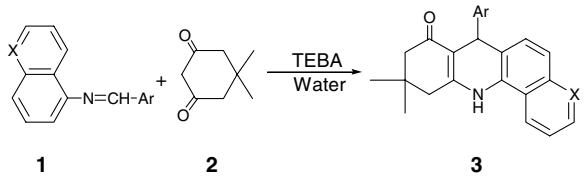
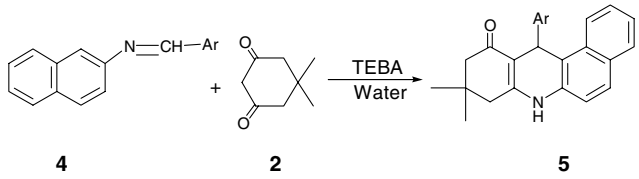


1 2 3

Scheme 1.



4 2 5

Scheme 2.

Table 1. Synthesis of **3** in water, catalyzed by TEBA[15]

Entry	Ar	X	Time (h)	Products	Yield (%)
1	4-ClC_6H_4	CH	12	**3a**	93
2	4-OHC_6H_4	CH	18	**3b**	92
3	4-$CH_3OC_6H_4$	CH	18	**3c**	89
4	4-BrC_6H_4	CH	12	**3d**	91
5	3,4-$(CH_3O)_2C_6H_3$	CH	18	**3e**	93
6	2-ClC_6H_4	CH	12	**3f**	98
7	4-ClC_6H_4	N	24	**3g**	81
8	4-OHC_6H_4	N	24	**3h**	84
9	4-$CH_3OC_6H_4$	N	24	**3i**	76
10	3,4-$OCH_2OC_6H_3$	N	24	**3j**	83
11	3,4-$(CH_3O)_2C_6H_3$	N	24	**3k**	82
12	2,4-$Cl_2C_6H_3$	N	18	**3l**	86

Table 2. Synthesis of **5** in water, catalyzed by TEBA[15]

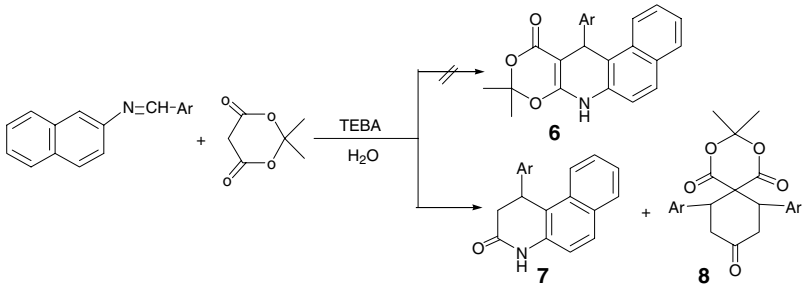
Entry	Ar	Time (h)	Products	Yield (%)
1	4-ClC_6H_4	3	**5a**	98
2	2-ClC_6H_4	3	**5b**	94
3	4-$CH_3OC_6H_4$	5	**5c**	97
4	4-BrC_6H_4	4	**5d**	87
5	3,4-$Cl_2C_6H_3$	2	**5e**	87
6	3,4-$(CH_3O)_2C_6H_3$	10	**5f**	96
7	3-CH_3O-4-OHC_6H_3	12	**5g**	99
8	2,4-$Cl_2C_6H_3$	2	**5h**	99
9	2-Thiophenyl	5	**5i**	98
10	3-ClC_6H_4	2	**5j**	96

In order to demonstrate the efficiency and the applicability of the present method, we performed the reaction of a variety of *N*-arylidenenaphthalen-1-amine or *N*-arylidenequinolin-5-amine with dimedone in water at 100 °C and in the presence of TEBA, which behaves as a phase transfer catalyst. As shown in Table 1, we can see a series of **1**, either bearing electron-withdrawing groups (such as halide) or electron-donating groups (such as hydroxyl group and alkoxyl group), reacting with **2** to give the corresponding products **3** in good yields under same reaction conditions. Therefore we concluded that the electronic nature of the substituents has no significant effect on this reaction.

As expected, when the *N*-arylidenenaphthalen-1-amine **1** was replaced by *N*-arylidenenaphthalen-2-amine **4** prepared by the reaction of aromatic aldehydes with naphthalen-2-amine, another series of 3,3-dimethyl-9-aryl-1,2,3,4,9,10-hexahydrobenzo[*a*]acridine-1-one derivatives **5** were obtained under the same reaction conditions (Scheme 2). The results are summarized in Table 2.

To expand the reaction scope of Schiff base with 1,3-dicarbonyl compounds, we tried the reaction of **4** with different 1,3-dicarbonyl compounds, especially alkyl chain compounds, such as 2,4-pentanedione and dibenzoylmethane. Surprisingly, we could not get the expected benzo[*f*]quinoline derivatives. According to the report,[16] the pK_a value of dimedone (5.2) is lower than those of the above tested compounds (2,4-pentanedione (9.0), dibenzoyl methane (9.0)).[17] We think that the pK_a of the active hydrogen in the 1,3-dicarbonyl compounds plays a critical role in this reaction. This stimulated us to find some other 1,3-dicarbonyl compounds with low pK_a as substrates. As a representative, we selected meldrum's acid (pK_a 4.3) to prove our assumption. To our delight, the reaction proceeded smoothly. However, the desired products **6** were not detected after all, but a series of benzo[*f*]quinoline derivatives **7** were obtained, accompanied with a little byproducts of **8** (Scheme 3). The results are summarized in Table 3.

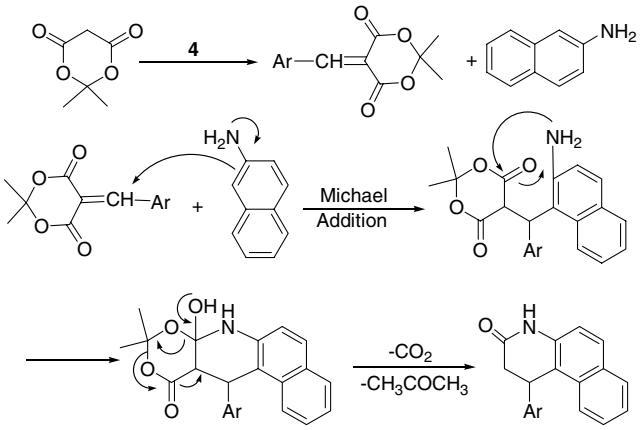
Although the detailed mechanism of the above reaction has not been clarified yet, the formation of benzo[*f*]quinoline derivatives **7** can be explained by a possible mechanism presented in Scheme 4, based on the reference[19] that reported that meldrum's acid readily lost CO_2 and acetone when heated.



Scheme 3.

Table 3. Synthesis of **7** and **8** in water, catalyzed by TEBA[18]

Entry	Ar	Time (h)	Products	Yield (%)	Products	Yield (%)
1	4-ClC_6H_4	13	**7a**	81	**8a**	8
2	4-BrC_6H_4	12	**7b**	74	**8b**	10
3	2-ClC_6H_4	12	**7c**	80	**8c**	8
4	3,4-$Cl_2C_6H_3$	10	**7d**	78	**8d**	10
5	2-Thiophenyl	10	**7e**	75	**8e**	11



Scheme 4.

In a further study, we found that 4-chlorophenyl-1,2,3,4-tetrahydrobenzo[*f*]quinolin-2-one **7a** was readily obtained when 4-chlorophenylmethylidenemeldrum's acid was treated with 2-aminonaphthalene in water at 100 °C in the presence of TEBA. It is possible to indicate from the result that the Michael addition reaction takes place in the mechanism mentioned above.

All the products were characterized by ^1H NMR, IR spectra and elemental analyses. The structures of **3h**, **5a**, **7a** and **8a** were further confirmed by X-ray diffraction analysis.[20] The molecular structures of **3h**, **5a**, **7a** and **8a** are shown in Figures 1–4, respectively.

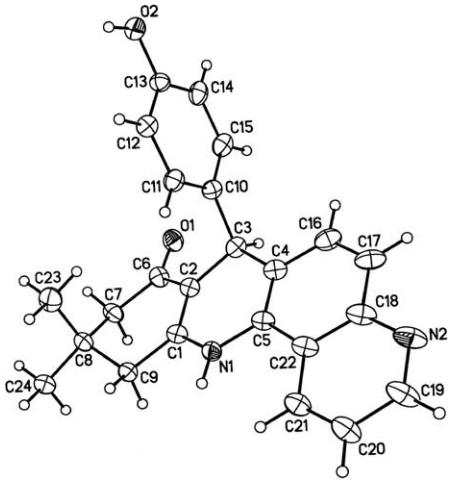


Figure 1. ORTEP diagram of **3h**.

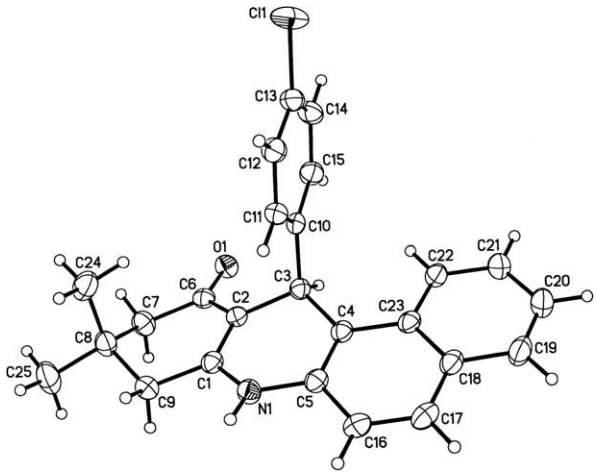


Figure 2. ORTEP diagram of **5a**.

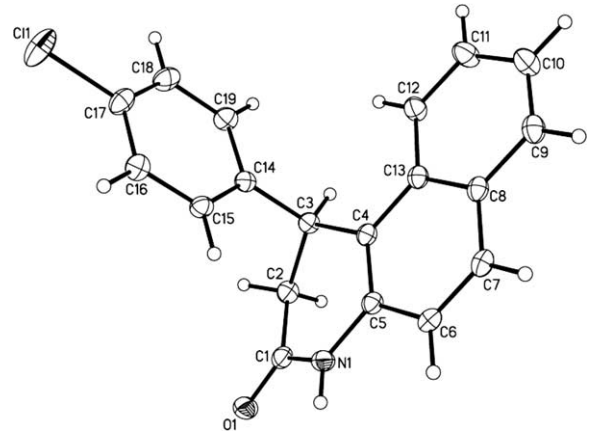


Figure 3. ORTEP diagram of **7a**.

In conclusion, we have developed a novel synthetic method for the synthesis of benzo[*c*]acridine, benzo[*a*]-acridine, pyrido[2,3-*c*]acridine and benzo[*f*]quinoline derivatives in good to excellent yields in aqueous medium. This method has the advantages of good yields, mild reaction conditions, easy work-up, inexpensive reagents and being environmentally friendly over the existing procedures.

Crystallographic data for the structures of **3h**, **5a**, **7a** and **8a** reported in this letter have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication with No. CCDC-279273, CCDC-279274, CCDC-279275 and CCDC-279276, respectively.

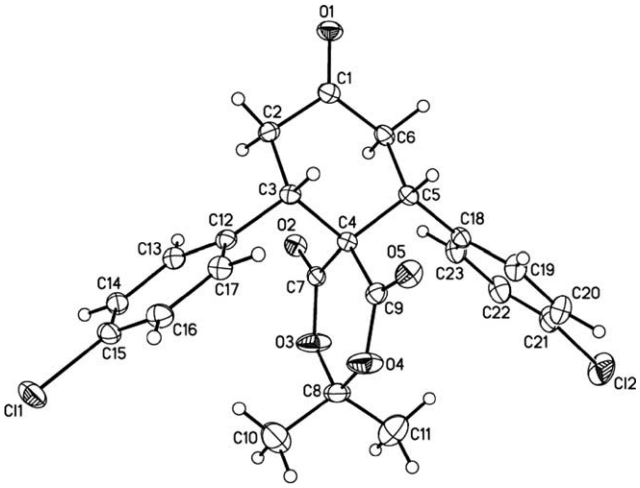


Figure 4. ORTEP diagram of **8a**.

Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

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15. The general procedure for **3** and **5** is presented as follows: A mixture of Schiff base **1** or **4** (2 mmol), dimedone **2** (2 mmol) and TEBA (0.1 g) was suspended in water (10 mL) and stirred at 100 °C for several hours. Upon completion, monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline powder was collected by filtration, washed with water and recrystallized from DMF and water mixture to give pure acridine derivatives **3** or **5**. Compound **3a**: mp 263–266 °C; ^{1}H NMR: δ 0.98 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.05 (d, $J = 16.0$ Hz, 1H, CH), 2.25 (d, $J = 16.0$ Hz, 1H, CH), 2.66 (d, $J = 16.8$ Hz, 1H, CH), 2.73 (d, $J = 16.8$ Hz, 1H, CH), 5.23 (s, 1H, CH), 7.18–7.28 (m, 5H, ArH), 7.46–7.53 (m, 2H, ArH), 7.57–7.60 (m, 1H, ArH), 7.83 (d, $J = 8.4$ Hz, 1H, ArH), 8.47 (d, $J = 8.4$ Hz, 1H, ArH), 9.31 (s, 1H, NH); IR (KBr, v, cm^{-1}): 3307, 2954, 1672, 1589, 1518, 1384, 1261, 1151, 1089, 1060, 1014, 850, 806, 756. Anal. Calcd for $C_{25}H_{22}ClNO$: C, 77.41; H, 5.72; N, 3.61. Found: C, 77.34; H, 5.88; N, 3.60. Compound **3h**: mp > 300 °C; ^{1}H NMR: 1.08 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.05 (d, $J = 16.0$ Hz, 1H, CH), 2.24 (d, $J = 16.0$ Hz, 1H, CH), 2.04 (d, $J = 17.2$ Hz, 1H, CH), 2.69 (d, $J = 17.2$ Hz, 1H, CH), 5.11 (s, 1H, CH), 6.65 (d, $J = 8.4$ Hz, 2H, ArH), 7.00 (d, $J = 8.4$ Hz, 2H, ArH), 7.49 (d, $J = 8.8$ Hz, 1H, ArH), 7.55 (d, $J = 8.8$ Hz, 1H, ArH), 7.57–7.59 (m, 1H, ArH), 8.84 (d, $J = 4.4$ Hz, 1H, ArH), 8.90 (d, $J = 8.4$ Hz, 1H, ArH), 9.12 (s, 1H, NH), 9.35 (s, 1H, OH). IR (KBr, v, cm^{-1}): 3286, 3197, 2957, 1693, 1569, 1490, 1415, 1382, 1262, 1248, 1155, 1066, 831, 790. Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.61; H, 5.87; N, 7.60. Compound **5a**: mp > 300 °C; ^{1}H NMR: 0.84 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.02 (d, $J = 16.0$ Hz, 1H, CH), 2.23 (d, $J = 16.0$ Hz, 1H, CH), 2.39 (d, $J = 16.4$ Hz, 1H, CH), 2.55 (d, $J = 16.4$ Hz, 1H, CH), 5.79 (s, 1H, CH), 7.19 (d, $J = 8.4$ Hz, 2H, ArH), 7.24 (d, $J = 8.4$ Hz, 2H, ArH), 7.30–7.34 (m, 2H, ArH), 7.40–7.44 (m, 1H, ArH), 7.79–7.82 (m, 2H, ArH), 7.90 (d, $J = 8.8$ Hz, 1H, ArH), 9.77 (s, 1H, NH). IR (KBr, v, cm^{-1}): 3257, 3076, 2956, 2935, 2873, 1684, 1635, 1578, 1540, 1519, 1500, 1429, 1387, 1258, 1248, 1150, 1086, 1013, 843, 820, 748. Anal. Calcd for $C_{25}H_{22}ClNO$: C, 77.41; H, 5.72; N, 3.61. Found: C, 77.28; H, 5.80; N, 3.71.
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Anal. Calcd for $C_{19}H_{14}ClNO$: C, 74.15; H, 4.58; N, 4.55. Found: C, 74.25; H, 4.56; N, 4.66. Compound **8a**: mp 208–209 °C; ^{1}H NMR: 0.62 (s, 6H, $2\times CH_3$), 2.53 (dd, $J = 14.0$ Hz, $J' = 4.4$ Hz, 2H, CH), 3.44 (t, $J = 14.0$ Hz, 2H, CH), 4.14 (dd, $J = 14.0$ Hz, $J' = 4.4$ Hz, 2H, CH), 7.18 (d, $J = 8.8$ Hz, 4H, ArH), 7.48 (d, $J = 8.8$ Hz, 4H, ArH); IR (KBr, v, cm^{-1}): 3060, 2999, 2924, 1759, 1727, 1595, 1492, 1417, 1388, 1374, 1310, 1286, 1245, 1196, 1091, 1065, 1013, 984, 912, 893, 839. Anal. Calcd for $C_{23}H_{20}Cl_2O_5$: C, 61.76; H, 4.51. Found: C, 61.82; H, 4.77.

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20. Crystal data for **3h**: $C_{24}H_{22}N_2O_2$; $M = 370.44$, orange-yellow block crystals, $0.72\times0.70\times0.42$ mm, tetragonal, space group $P\,43\,21\,2$, $a = 11.7044(11)$, $b = 11.7044(11)$, $c = 28.975(3)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 3969.3(7)^3$, $Z = 8$, $D_c = 1.240$ g cm^{-3}. $F(000) = 1568$, μ(Mo Kα) = 0.079 mm^{-1}. Intensity data were collected on Rigaku Mercury diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71070$ Å) using ω scan mode with $3.24° < \theta < 25.35°$. 2154 unique reflections were measured and 2128 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to $R = 0.0356$ and $wR = 0.0855$. Crystal data for **5a**: $C_{25}H_{22}ClNO$; $M = 387.89$, colourless block crystals, $0.40\times0.35\times0.12$ mm, monoclinic, space group $P2_1/n$, $a = 10.4242(14)$, $b = 11.777(2)$, $c = 16.173(3)$ Å, $\beta = 91.024(5)°$, $V = 1985.1(5)$ Å^3, $Z = 4$, $D_c = 1.298$ g cm^{-3}. $F(000) = 816$, μ(Mo Kα) = 0.208 mm^{-1}. Intensity data were collected on a Rigaku Mercury diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71070$ Å) using the ω scan mode with $3.06° < \theta < 25.35°$. 3622 unique reflections were measured and 3006 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to $R = 0.0571$ and $wR = 0.1186$. Crystal data for **7a**: $C_{19}H_{14}ClNO$; M = 307.76, colourless block crystals, $0.40\times0.35\times0.16$ mm, monoclinic, space group $P2_1/n$, $a = 7.5826(12)$, $b = 9.0381(11)$, $c = 21.150(3)$ Å, $\beta = 92.333(4)°$, $V = 1448.3(4)$ Å^3, $Z = 4$, $D_c = 1.411$ g cm^{-3}. $F(000) = 640$, μ(Mo Kα) = 0.264 mm^{-1}. Intensity data were collected on a Rigaku Mercury diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71070$ Å) using the ω scan mode with $3.61° < \theta < 27.48°$. 3318 unique reflections were measured and 2854 reflection with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to $R = 0.0506$ and $wR = 0.1121$. Crystal data for **8a**: $C_{23}H_{20}Cl_2O_5$; $M = 447.29$, colourless block crystals, $0.60\times0.59\times0.20$ mm, monoclinic, space group $c2/c$, $a = 37.432(5)$, $b = 9.8988(10)$, $c = 11.5926(14)$ Å, $\beta = 96.534(4)°$, $V = 4267.9(9)$ Å^3, $Z = 8$, $D_c = 1.392$ g cm^{-3}. $F(000) = 1856$, μ(Mo Kα) = 0.337 mm^{-1}. Intensity data were collected on a Rigaku Mercury diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71070$ Å) using the ω scan mode with $3.07° < \theta < 27.48°$. 4857 unique reflections were measured and 4486 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to $R = 0.0477$ and $wR = 0.1061$.