Asian Journal of Chemistry; *Vol. 23, No. 11 (2011), 4900-4902*

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

p-Dodecylbenzene Sulfonic Acid Catalyzed Simple and Efficient Synthesis of 1,8-Dioxo-decahydroacridines in Aqueous Media

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(*Received*: 19 October 2010; *Accepted*: 20 July 2011) AJC-10175

p-Dodecylbenzene sulfonic acid (DBSA)-catalyzed synthesis of new fluorinated 1,8-dioxo-decahydroacridines is achieved *via* one-pot, three component condensation of aromatic aldehydes (**1**), 5,5-dimethyl-1,3-cyclohexanedione (**2**) and 4-fluoroaniline (**3**) in aqueous media. This method provides several advantages such as neutral and mild condition, high to excellent yield and simple work-up.

Key Words: Surfactant, *p*-Dodecylbenzene sulfonic acid, 1,4-Dihydropyridine, 4-Fluoroaniline, 1,8-Dioxo-decahydroacridines.

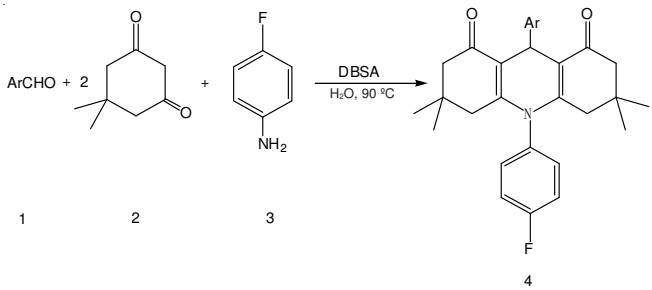
INTRODUCTION

In recent years, 1,4-dihydropyridines (1,4-DHPs) and their derivatives have attracted much attention due to their significant biological activities in the treatment of cardiovascular disease[1,2] as calcium channel blockers[3-6]. 1,8-Dioxo-9-aryl-10-aryl-decahydroacridines and their derivatives are polyfunctionalized 1,4-dihydropyridine derivatives. Therefore the preparation of such heterocycles received an increased attention to synthetic organic chemists and biologists.

Several new methods have been developed including the use of microwave[7-9], ionic liquid[10], silica-bonded S-sulfonic acid (SBSSA)[11], tris(pentafluorophenyl)borane[$B(C_6F_5)_3$] [12], heterogeneous catalyst: amberlyst-15[13], proline[14], concentrated hydrochloric acid[15], high temperature in refluxing solvent and so forth. In addition, *p*-dodecylbenzene sulfonic acid was also employed but the products were restricted to *p*-toluidine derivatives[16]. Some of these methods have limitations such as poor yields, cumbersome workup procedure and expensive catalyst and the use of organic solvent. Thus the pursuance of more convenient and practical synthetic methods for these compounds still remains an active research area.

With the increase of environmental pollution, searching for nontoxic reaction conditions to carry out various organic transformations is of great importance. Water as a safe, cheap and environmental benign solvent has received much attention. However, water has poor ability to solve the organic substrate and makes some catalysts decompose or loses activity. These major drawbacks limit its application in organic reaction. Using phase-transfer catalysis (PTC) or surfactant in aqueous media has solved this problem[16-18]. Phase-transfer catalysis and surfactant contain hydrophobic and hydrophilic groups, so it can present in water and organic solvent to catalyze the organic reaction.

Generally the introduction of fluorine into the compound can improve its properties including enhanced binding interactions, metabolic stability, changes in physical properties and selective reactivates. The C-F bond is much stronger than C-H bond, so the fluorinated compounds tend to be more resistant to metabolic degradation and the introduction of fluorine also generally confers increased lipophilicity. Many fluorinated compounds are already used as pharmaceuticals and more are being developed[19]. In view of these attractions, synthesizing the 1,8-dioxodecahydroacrid-ines derivatives, which contain fluorine is of our interest (**Scheme-I**).



Scheme-I

EXPERIMENTAL

Melting points were determined on a XT-4 microscopic melting-point spectrometer and are uncorrected. Infrared (IR)

spectra were recorded on a BIO-RADFTS-40 analyzer in KBr. ^{1}H NMR spectra were obtained from solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard using a Bruker AVANCEIII600-MHz spectrometer. Elemental analyses were carried out using CE-440 elemental analyzer. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck).

General procedure for preparation of 4a-j: Aromatic aldehydes(1 mmol), 5,5-dimethyl-1,3-cyclohexanedione(2 mmol), 4-fluoroaniline (1 mmol) and *p*-dodecylbenzene sulfonic acid (DBSA) (0.1 mmol) were stirred at 90 ºC in water (20 mL) for 2 h. Reaction completion was checked *via* TLC. The mixture was filtered, washed and dried. Then, the product was further purified by column chromatography over silica gel using CH_2Cl_2-EtOAC (6:1) and got the light-yellow solid. The physical and spectra data of the compounds 1,8-dioxo-decahydroacridines are as follows.

10-(4-Fluorophenyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (4a): M.p. 236-238 ºC. IR (cm^{-1}): 2959, 1750, 751. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.83 (s, 6H), 0.98 (s, 6H), 1.83 (d, 2H, *J* = 17.4 Hz), 2.09 (d, 2H, *J* = 17.4 Hz), 2.16 (d, 2H, *J* = 16.2 Hz), 2.22 (d, 2H, *J* = 16.2 Hz), 5.30 (s, 1H), 7.13 (d, 1H, *J* = 7.2 Hz), 7.26 (d, 4H, *J* = 7.8 Hz), 7.23 (m, 2H), 7.43 (d, 2H, *J* = 7.2 Hz).

9-(4-Chlorophenyl)-10-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (4b): M.p. 278-280 ºC. IR (cm^{-1}): 2961, 1739, 804,742. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.83 (s, 6H), 0.98 (s, 6H), 1.83 (d, 2H, *J* = 8.0 Hz), 2.07 (d, 2H, *J* = 17.4 Hz), 2.15 (d, 2H, *J* = 16.2 Hz), 2.22 (d, 2H, *J* = 16.2 Hz), 5.25 (s, 1H), 7.23 (m, 4H), 7.28 (d, 2H, *J* = 15.0 Hz), 7.37 (d, 2H, *J* = 8.4 Hz).

9-(3-Chlorophenyl)-10-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (4c): M.p. 248-250 ºC. IR (cm^{-1}): 2960, 1750, 875, 771. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.85 (s, 6H), 0.99 (s, 6H), 1.85 (d, 2H, *J* = 17.4 Hz), 2.08 (d, 2H, *J* = 17.4 Hz), 2.18 (d, 2H, *J* = 16.8 Hz), 2.23 (d, 2H, *J* = 16.2 Hz), 5.27 (s, 1H), 7.11(d, 1H, *J* = 8.4 Hz), 7.20 (t, 1H, *J* = 15.6 Hz), 7.24 (m, 3H), 7.29 (m, 1H), 7.37 (t, 2H, *J* = 15.0 Hz).

9-(2-Chlorophenyl)-10-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (4d): M.p. 240-243 ºC. IR (cm^{-1}): 2954, 1750, 863, 749. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.87 (s, 6H), 0.95 (s, 6H), 1.82 (d, 2H, *J* = 17.4 Hz), 1.99 (d, 2H, *J* = 17.4 Hz), 2.12 (d, 2H, *J* = 16.2 Hz), 2.17 (d, 2H, *J* = 16.2 Hz), 5.45 (s, 1H), 7.08(m, 1H), 7.24(m, 5H), 7.34 (m, 1H), 7.21 (d, 1H, *J* = 7.8 Hz).

9-(2,4-Dichlorophenyl)-10-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (4e): M.p. 274-275 ºC. IR (cm^{-1}): 2950, 1750, 861, 744. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.88 (s, 6H), 0.96 (s, 6H), 1.82 (d, 2H, *J* = 17.4 Hz), 1.99 (d, 2H, *J* = 17.4 Hz), 2.12 (d, 2H, *J* = 16.8 Hz), 2.18 (d, 2H, *J* = 16.2 Hz), 5.41 (s, 1H), 7.20 (d, 1H, *J* = 1.8 Hz), 7.22 (d, 1H, *J* = 1.8 Hz), 7.25 (m, 4H), 7.66 (d, 1H, *J* = 8.4 Hz).

10-(4-Fluorophenyl)-3,3,6,6-tetramethyl-9-(3-nitrophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (4f): M.p. 276-279 ºC. IR (cm^{-1}): 2961, 1750, 852. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.79 (s, 6H), 0.98 (s, 6H), 1.86 (d, 2H, *J* = 17.4 Hz), 2.12 (t, 4H, *J* = 35.4 Hz), 2.22 (d, 2H, *J* = 16.8 Hz), 5.35 (s, 1H), 7.30 (m, 4H), 7.43 (t, 1H, *J* = 15.6 Hz), 7.98 (m, 2H), 8.18(m, 1H).

10-(4-Fluorophenyl)-3,3,6,6-tetramethyl-9-(4-nitrophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (4g): M.p. 286-288 ºC. IR (cm^{-1}): 2960, 1733, 888. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.81 (s, 6H), 0.97 (s, 6H), 1.84 (d, 2H, *J* = 17.4 Hz), 2.07 (d, 2H, *J* = 18.0 Hz), 2.13 (d, 2H, *J* = 16.2 Hz), 2.21 (d, 2H, *J* = 16.2 Hz), 5.34 (s, 1H), 7.26 (m, 4H), 7.59 (d, 2H, *J* = 9.0 Hz), 8.13 (d, 2H, *J* = 8.4 Hz).

10-(4-Fluorophenyl)-3,3,6,6-tetramethyl-9-*p*-tolyl-3,4,6,7-tetrahydroacridine-1,8(2H, 5H,9H,10H)-dione (4h): M.p. 252-255 ºC. IR (cm^{-1}): 2960, 1739, 743. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.84 (s, 6H), 0.98 (s, 6H), 1.83 (d, 2H, *J* = 16.8 Hz), 2.07 (d, 2H, *J* = 17.4 Hz), 2.18 (d, 2H, *J* = 16.2 Hz), 2.22 (d, 2H, *J* = 16.2 Hz), 2.28 (s, 3H), 5.25 (s, 1H,C H), 7.07 (d, 2H, *J* = 8.4 Hz), 7.24 (m, 4H), 7.32 (d, 2H, *J* = 8.4 Hz).

10-(4-Fluorophenyl)-9-(4-hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (4i): M.p. 261-266 ºC. IR (cm^{-1}): 3425, 2961, 1749, 1258, 751. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.85 (s, 6H), 0.98 (s, 6H), 1.83 (d, 2H, *J* = 17.4 Hz), 2.07 (d, 2H, *J* = 17.4 Hz), 2.18 (d, 2H, *J* = 16.2 Hz), 2.23 (d, 2H, *J* = 16.2 Hz), 3.94 (s, 3H), 5.20 (s, 1H), 5.47 (s, 1H), 6.72 (d,d,1H, J_1 = 6.6, J_2 = 1.8 Hz), 6.80 (d, 1H, *J* = 7.8 Hz),7.17 (d, 1H, *J* = 1.8 Hz), 7.23 (m, 4H).

10-(4-Fluorophenyl)-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (4j): M.p. 242-244 ºC. IR (cm^{-1}): 2951, 1683, 1219, 817. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.84 (s, 6H), 0.97 (s, 6H), 1.83 (d, 2H, *J* = 17.4 Hz), 2.07 (d, 2H, *J* = 17.4 Hz), 2.16 (d, 2H, *J* = 16.2 Hz), 2.22 (d, 2H, *J* = 16.2 Hz), 3.77 (s, 3H) 5.23 (s, 1H), 6.81 (d, 2H, *J* = 8.4 Hz), 7.24 (m, 4H), 7.34 (d, 2H, *J* = 9.0 Hz).

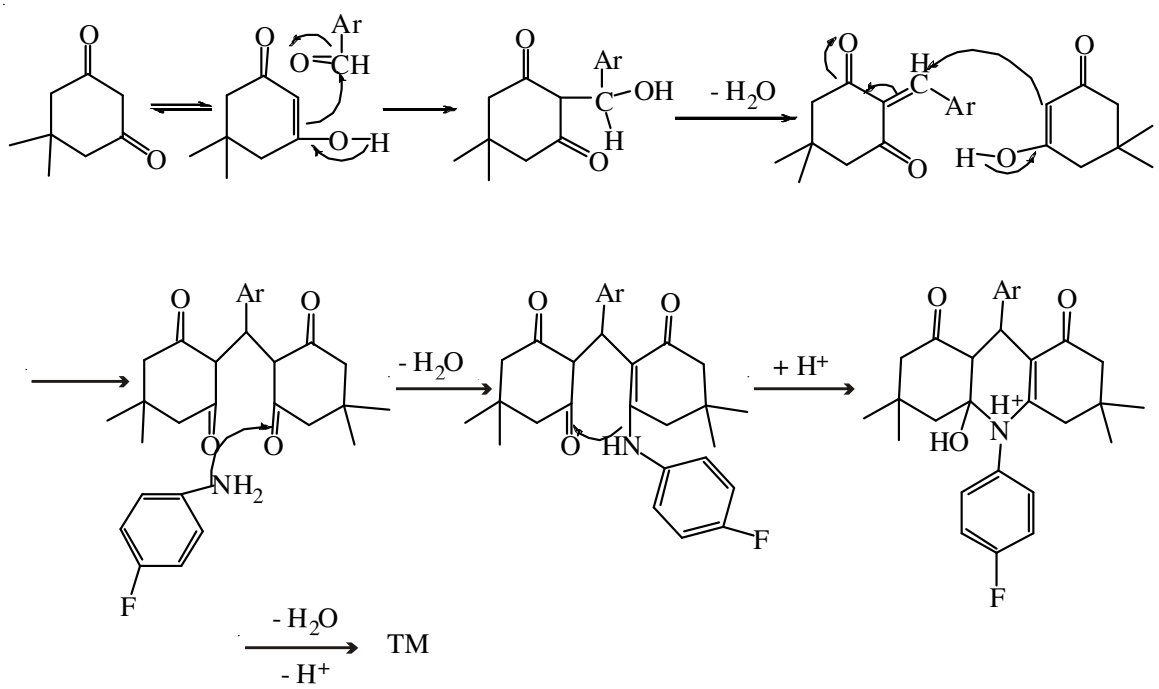
RESULTS AND DISCUSSION

We initiate our investigation catalyzed by polyoxyethylene lauryl ether sodium sulfate (AES), benzyltrimethyl ammonium bromide and *p*-dodecylbenzene sulfonic acid (DBSA) respectively. These reactions were in poorer yields catalyzed by AES and benzyltrimethyl ammonium bromide than catalyzed by DBSA. So Using DBSA as a Brfnsted acid-surfactant-combined catalyzing the synthesis of 1,8-dioxo-decahydroacridines attracted our interest.

On one hand, the long chain of DBSA has the effect of emulsification and dispersion of the substrate. On the other hand, DBSA also catalyzes the reaction as a proton acid. With the two aspects, DBSA plays an important role in the synthesis of 1,8-dioxo-decahydroacridines.

Indeed, the amount of catalyst had a certain extent influence on the reaction yield. Taking the synthesis of compound **4a** for example, increasing the amount of the catalyst to 5, 10 and 15 mol % resulted in increasing the reaction yield to 92, 95 and 95 %. 10 mol % of DBSA was found to be a good amount.

To determine the scope of our protocol, a number of available aromatic aldehydes having both electron-donating and



Scheme-II

electron-withdrawing groups were condensed with 5,5-dimethyl-1,3-cyclohexanedione and 4-fluoroaniline. All of them were equally facile for the reaction and reacted smoothly in good to excellent yields. All of results are shown in Table-1. All the new compounds were well characterized by melting point, IR and ^{1}H NMR.

TABLE-1
SYNTHESIS OF 1,8-DIOXO-DECAHYDROACRIDINES

Entry	Comp	Ar	Yields (%)*
1	**4a**	C_6H_5	95
2	**4b**	4-ClC_6H_4	97
3	**4c**	3-ClC_6H_4	96
4	**4d**	2-ClC_6H_4	90
5	**4e**	2, 4-$Cl_2C_6H_3$	96
6	**4f**	3-$NO_2C_6H_4$	72
7	**4g**	4-$NO_2C_6H_4$	97
8	**4h**	4-$CH_3C_6H_4$	96
9	**4i**	4-OH-3-$CH_3OC_6H_3$	98
10	**4j**	4-$CH_3OC_6H_4$	94

*Yields refer to isolated products

On the basis of reported literature[16], it is presumed that the possible mechanism is as follows (**Scheme-II**). In the mechanism, the DBSA acts as a weak lewis acid catalyst and promotes this reaction.

In conclusion, we have developed a simple, eco-friendly, cost-effective and efficient synthetic protocol for the synthesis of the 1,8-dioxodecahydroacridines derivatives. *p*-Dodecylbenzene sulfonic acid is found to be an inexpensive and effective catalyst for this reaction. Using water as solvent makes this protocol eco-friendly and economically. All of these factors justify that this procedure is superior to the existing methods. Current studies are ongoing in our laboratory in order to gain the better pharmacological properties of 1,8-dioxodecahydroacridines derivatives, which contain fluorine.

ACKNOWLEDGEMENTS

This project was supported by the Natural Science Foundation of Hebei Province (B2011201174, B2009000161), Science and Technology Commission of Hebei Province (05215104) and Open Fund of Laboratory of Chemical Biology of Hebei Provincem (No. 09265631D-7).

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