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Solvent-Free Neat Synthetic Route to Tetrahydroacridinones

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ABSTRACT: *An environmentally benign approach for the synthesis of acridines using inorganic solid supports and "neat reaction" technology is described. These methodologies completely eliminate the use of solvent during the course of reaction. Moreover, microwave-assisted reactions reduce the reaction time from hours to minutes with improved yield.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:138–141, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20080

INTRODUCTION

Acridines and its derivatives inhibit HIV-1 reverse transcriptase by intercalating the template–primer hybrid [1]. They are also well known as antimicrobials [2,3] and antitumor agents [4,5] and are used for the treatment of urinary incontinence [6]. The title compounds under investigation are also associated with the structural aspects of dihydropyridine (DHP) and quinoline moieties. The chemical modifications carried out on the DHP ring [7] such as the presence of different substituents [8] or heteroatoms [9] have allowed expansion of the structure activity relationship and afforded some insights into the molecular interactions at the receptor level. 1,4-DHPs are well known because of their pharmacological profiles [10,11]. Furthermore, hexahydroquinolines play an important role in medicinal chemistry as anxiolytic [12] and memory enhancers [13] and show marked positive inotropic effect [14]. An essential prerequisite for the therapeutic application prompted us to undertake the title investigation.

We herein report a method that allows the rapid, facile synthesis of acridines-related structures and does not rely on the conventional procedure [15]. Instead, our procedure involves a microwave-promoted solvent-free variation of acridine synthesis. The application of microwave irradiations (MWI) in organic synthesis has been the focus of considerable interest in recent years. Chemical technology is increasingly facing eco-environmental pressure and is thus obliged to re-examine, conventional methodologies to seek ways of developing and applying more efficient eco-friendly strategies. One of the areas wherein substantial progress has been seen in our laboratory [16,17] is the microwave-assisted solid support synthesis. These heterogeneous reactions are facilitated by reagents immobilized on porous solid supports (alumina, montmorillonite, bentonite, etc.). These dry media reactions [18] have advantages over conventional solution phase reactions owing to dispersion of active reagent sites, catalysis, associated selectivity, and recyclability. The other one is the "neat reaction" technology. "Neat Reaction" [7] is an alternative solvent-free approach in which a mixture of reactants without any solvent is irradiated under microwaves. This technique is further beneficial as it obviates the requirement of the solvent for the adsorption of reactants and elution of product in pre- and post-reaction stages. Such solvent-free synthesis is advantageous for environmental reasons and offers the benefits of shorter reaction time along with enhanced yield especially when coupled with microwaves [19].

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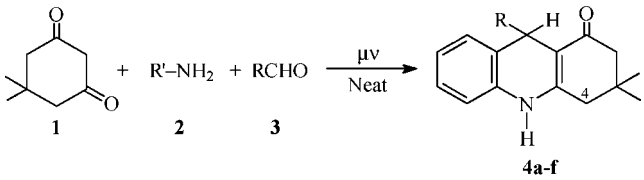
Keeping in view the therapeutic importance and physiological properties of the acridine, quinoline, and dihydropyridine moieties coupled with microwave for environmentally benign synthesis, it was thought worthwhile to develop a facile one-pot synthetic route using neat reaction conditions under microwave.

RESULTS AND DISCUSSION

Various reported methods of acridines synthesis involve Bernthsen [20] synthesis in which diphenylamine is condensed with aromatic carboxylic acids, Ullman reaction to form diphenylamine-2-carboxylic acids that can cyclize to the corresponding acridone. Harsh reductive and oxidative conditions are then required to form the acridines derivatives [21]. Another one is the synthesis of decahydroacridinones [22]. Also in close association with acridines, the structure is the linearly fused DHPs for which numerous synthetic modes have been reported [23,24]. Quite well known is the Hantzsch synthesis that involves the reaction of an aldehyde, β-ketoester, and concentrated aqueous ammonia [25]. Cyclic 1,3-diketone when condensed with aldehyde and β-amino crotonate affords a bicyclic 4-aryl-1,4-dihydropyridine with the ester substitution at 3-position [26]. The present communication reports the synthesis of novel acridine-type-related structures related to 1,4-DHP as a microwave-assisted extension leading to the linearly fused tricylic 1,4-DHP. Close observation of the structure reveals that it is a tetrahydroacridinone moiety that incorporates the 1,4-DHP ring. Classically [27], the synthesis is carried out by refluxing equimolar amounts of primary aromatic amines **2** in absolute ethanol (20 mL) with 5,5-dimethylcyclohexan-1,3-dione (dimedone) **1** and appropriate aromatic or heteroaromatic aldehyde **3** for 5–10 h in 65–75% yield (Scheme 1). This procedure although conventional yet suffers from some setbacks as it requires long reaction time, excessive solvent, gives low yield and in the present case, instead of ammonia, ammonium acetate, or alkyl β-crotonates, aromatic amines are used. In another experiment, same amounts of all reactants were adsorbed over basic [28]/neutral [29] alumina which gave the same product in 8–12 min in 70–80% yield. Results obtained were better in basic alumina than neutral alumina. But when an equimolar mixture of neat reactants was irradiated under microwaves [30] without any solvent, it proved to be a high-yielding protocol. The reaction completed within 5 min with 82–87% yield (Table 1). The structures were established on the basis of spectroscopic data (Table 2). In IR, the



4a R' = Phenyl, R = Phenyl
4b R' = 3-Chloro, 4-fluoro-phenyl, R = Phenyl
4c R' = 4-Chlorophenyl, R = Benzo[1,3]dioxol-5-yl
4d R' = α-Naphthyl, R = Phenyl
4e R' = 3-Methylphenyl, R = 3-Indolyl
4f R' = 4-Nitrophenyl, R = 3-Quinolinyl

SCHEME 1

appearance of band around 3430 cm^{-1} due to secondary amine, and around 1630 cm^{-1} due to C=C stretching and in ^1H NMR, the presence of signal at 5.3 δ due to methine proton and NH peak at 6.7–8 δ confirmed the formation of products. Further, the observation that product formed has the linear structure, i.e. an acridine derivative is evidenced by ^1H NMR spectra as the 4-H and 9-NH are not coupled.

The reaction can be postulated as the Knoevenagel condensation of aldehyde and dimedone followed by the Michael addition of the formed arylidene dimedone intermediate with primary aromatic amine and subsequent ring closure to afford the corresponding tetrahydroacridinone derivative in which the DHP ring is enclosed.

In conclusion, we have developed a facile, one-pot condensation solvent-free route to tetrahydroacridinone derivatives incorporating the DHP system. This is developed as an extension of Hantzsch synthesis as it has ability to withstand the variations in the 1,3-diketone, carbonyl, and amine part.

EXPERIMENTAL SECTION

Melting points were taken in Thomas Hoover melting point apparatus and were uncorrected. IR (KBr) spectra (ν in cm^{-1}) were obtained on a Perkin-Elmer 1710 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ on FT NMR Hitachi R-600 spectrometer operating at 60 MHz using TMS as internal standard (chemical shifts in δ ppm). Elemental analyses were performed on Heraeus CHN Rapid Analyzer. A Kenstar (model no. OM 9925E) household microwave oven (2450 MHz, 850 W) was used for the experiment. The purity of compounds was checked on silica gel coated aluminum plates (Merck).

TABLE 1 Time/Yield of Compounds **4a–h**

Compd. No.	R′	R	Melting Point (°C)	Conventional Solution Phase Method A		Microwave					
						Solid Support Method B				Neat Method C	
						Basic Alumina		Neutral Alumina			
				t(h)	Yield (%)	t(min)	Yield (%)	t(min)	Yield (%)	t(min)	Yield (%)
4a	Phenyl	Phenyl	192–194	7	73	10	78	10.5	78	2	85
4b	3-Chloro-4-fluoro phenyl	Phenyl	278–280	6	72	10	75	10	76	2	84
4c	4-Chloro-phenyl	Benz[1,3] dioxol-5-yl	180–182	5.5	75	9	80	10	78	1	85
4d	α-Naphthyl	Phenyl	260–262[27]	4	62	8.5	80	9	75	2	87
4e	3-Methyl-phenyl	3-Indolyl	130–132	8	68	12	75	14	76	4	83
4f	4-Nitro-phenyl	3-Quinolinyl	202–204	10	65	12	74	15	75	5	82

General Procedure for the Synthesis of 9-Aryl-1,2,3,4-tetrahydro-3,3-dimethyl-9H, 10H-acridin-1-one

Method A : Conventional Solution Phase. A mixture of dimedone **1** (0.01 mol), primary aromatic amine **2** (0.01 mol), and aromatic or heteroaromatic aldehyde **3** (0.01 mol) in absolute ethanol (20 mL) was refluxed for the appropriate time. The progress of the reaction was monitored through the TLC examination. Upon completion of reaction, the reaction mixture was cooled and concentrated. The solid obtained was filtered and recrystallized from ethanol.

Method B : Solid Support Microwave. To the solution of dimedone **1** (0.01 mol), primary aromatic amine **2** (0.01 mol) and aromatic or heteroaromatic aldehyde **3** (0.01 mol) in ethanol, neutral/basic alumina (15 g) was added with stirring and air dried. It was then placed in an alumina bath used as heat sink and subjected to microwave irradiation (MWI) intermittently (approx. bulk temperature reached ~80–100°C). The progress of reaction was monitored by the TLC examination. Upon completion of the reaction, the product was eluted from chloroform. Recovering the solvent under reduced pressure the solid obtained was then recrystallized from ethanol.

Method C: Microwave Neat Synthesis. A mixture of dimedone **1** (0.01 mol), primary aromatic amine **2** (0.01 mole), and aldehyde **3** (0.01 mole) was taken in an Erlenmeyer flask. This was subjected to MWI intermittently (approx. bulk temperature reached ~120–140°C). Reaction progress was

TABLE 2 Spectroscopic Data of Compounds **4a–f**

Compd. No.	IR (KBr, ν_{max} cm^{-1})		^1H NMR ($CDCl_3$, δ, ppm)
	NH	C=C	
4a	3448	1626	1.25 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.22 (s, 2H, CH_2), 2.40 (s, 2H, CH_2), 5.28 (s, 1H, CH), 6.18 (s, 1H, NH), 6.75–7.35 (m, 9H, Ar-H)
4b	3450	1643	0.98 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.03 (s, 2H, CH_2), 2.17 (s, 2H, CH_2), 5.32 (s, 1H, CH), 7.11–7.37 (m, 8H, Ar-H and NH)
4c	3429	1622	1.01 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.13 (s, 2H, CH_2), 2.34 (s, 2H, CH_2), 5.35 (s, 1H, CH), 6.03 (s, 2H, OCH_2O), 6.91–7.45 (m, 6H, Ar-H and N-H)
4d	3425	1625	1.07 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 2.13 (s, 2H, CH_2), 2.61 (s, 2H, CH_2), 5.36 (s, 1H, CH), 7.04–8.08 (m, 11H, Ar-H), 8.32 (s, 1H, NH)
4e	3440	1630	1.03 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.13 (s, 2H, CH_2), 2.44 (s, 2H, CH_2), 2.52 (s, 3H, CH_3), 5.44 (s, 1H, CH), 6.42–7.45 (m, 10H, Ar-H and N-H)
4f	3435	1638	1.12 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.22 (s, 2H, CH_2), 2.43 (s, 2H, CH_2), 5.42 (s, 1H, CH), 7.01–7.45 (m, 9H, Ar-H and N-H)

monitored by the TLC. Upon completion of reaction, the reaction mixture was cooled, triturated with ethanol, and filtered. The solid obtained was recrystallized from ethanol.

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[29] Aluminum oxide neutral, Brockmann I (Aldrich Chem Co., cat. no. 19, 997-4, ~150 mesh, 58 Å, Surface area 155 m^2/g).

[30] Microwave irradiations were carried out in a Kenstar microwave oven, model no. OM 9925E (2450 MHz, 800 W).