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Ceric ammonium nitrate (CAN) catalyzed synthesis of N-substituted decahydroacridine-1,8-diones in PEG

Mazaahir Kidwai *, Divya Bhatnagar

Green Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110 007, India

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ABSTRACT

Polyethylene glycol (PEG) was found to be an inexpensive non-toxic and effective medium for the one-pot synthesis of N-substituted decahydroacridine-1,8-diones in the presence of ceric ammonium nitrate (CAN) as the catalyst in high yields. Also, the solvent system can be recovered and reused; making this protocol economically and potentially viable.

1. Introduction

Substituted acridines have been used as antimalarials[1] for many years quite successfully and several of them have exhibited excellent results in chemotherapy of cancer.[2] These derivatives are frequently used in the industry, especially for the production of dyes.[3] Besides these properties, analogues of acridine have also been shown to have very long lasting efficiencies and have interesting electrochemical behavior[4] of heterocyclic compounds and in the interaction with DNA.[5] In view of the above-mentioned significance, the synthesis of this class of compounds under mild reaction conditions is of importance. Some methods are available in the literature for the synthesis of these acridine compounds from aldehydes, dimedone, and different anilines or ammonium acetate via traditional heating in organic solvents,[6] in water catalyzed by TEBAC (benzyl tri ethyl ammonium chloride),[7] under microwave irradiation[8] and using ionic liquids.[9] 9,10-Diarylacridine-1,8-diones could also be prepared using *p*-dodecylbenzenesulfonic acid (DBSA) in water.[10] However it should be noted that only *p*-toluidine was selected as a substrate.[10] The other substituted anilines either did not react or gave low yields, especially the anilines containing electron-withdrawing groups. Furthermore most of these methodologies do not meet the requirement of green chemistry as most of these reactions tend to use expensive reagents which are difficult to recover and recycle in volatile organic solvents which are a threat to the environment due to their pyrophoric nature, volatility, and poor recovery. Ionic liquids which have been used for the synthesis of such compounds[11] require tedious preparation and their environmental safety is still debatable.

Development of a synthetic protocol that is devoid of the above-mentioned problems and yet nature friendly, simple, efficient, and cost effective remains an ever challenging objective.

Recently, polyethylene glycol (PEG) is found to be an interesting solvent system.[12] It is a non-toxic, inexpensive, non-ionic liquid solvent of low volatility. PEG and its monomethyl ethers are inexpensive, thermally stable, recoverable, and non-toxic media for phase transfer catalysts.[13,14] PEG is a biologically acceptable polymer which has been used extensively in drug delivery and in bioconjugates as tools for diagnostics. It is being extensively used in organic substrates.[13,14]

Ceric(IV) ammonium nitrate has emerged as an important reagent for the construction of carbon–carbon and carbon–heteroatom bonds.[15] In addition, many advantages such as excellent solubility in water, cost-effectiveness, eco-friendly nature, easy handling, high reactivity, and easy work-up procedures make CAN a potent catalyst in organic synthesis. Besides, CAN is able to catalyze various organic transformations not only based on its electron transfer capacity but also with its Lewis acidic property.[16]

The environmentally benign nature of PEG and the versatility of CAN encouraged us to couple them together and study their utility in the synthesis of N-substituted decahydroacridine-1,8-diones. This is a paradigm shift in the formation of N-substituted decahydroacridine-1,8-diones, both in the context of green chemistry and

* Corresponding author. Tel./fax: +91 1127666235.
E-mail address: kidwai.chemistry@gmail.com (M. Kidwai).

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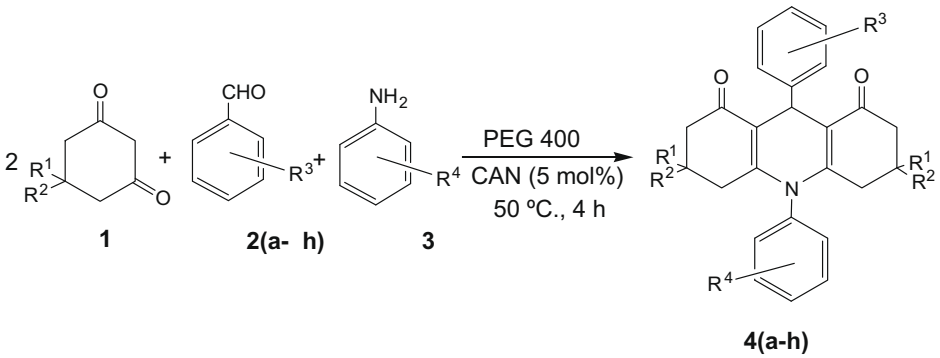

Scheme 1.

the ease, generality, and simplicity of the procedure. Waste generation and side products are largely avoided, and the products can be formed in high yield and purity.

In continuation of our studies in developing cheap and environmentally benign methodologies for organic synthesis,[17] we reveal herein report for the first time the synthesis of N-substituted decahydroacridine-1,8-diones using PEG-400 as a solvent and employing CAN as the catalyst (Scheme 1).

2. Results and discussion

In the initial studies the reaction between cyclohexadione (2 mmol), benzaldehyde (1 mmol), and aniline (1 mmol) was performed in traditional organic solvent (EtOH, Fig. 1). The reaction mixture was stirred for 18 h at 50 °C to obtain 60% of N-substituted decahydroacridine-1,8-dione **4a**, whereas the same reaction in the presence of PEG-400 as an environmentally friendly medium provided 91% of **4a** (Fig. 1) in only 8 h. Various solvents were tried for the same reaction and the results are summarized in Figure 1. PEGs were found to be the best media for this reaction.

To further improve the yield and to optimize the reaction conditions, the same reaction was carried out in the presence of 2 mol % of CAN under similar conditions. A tremendous improvement was observed and the yield of **4a** was increased up to 95% after stirring the mixture for only 6 h. With this optimistic result in hand, we further investigated the best reaction conditions by using different amounts of CAN. An increase in the quantity of CAN from 2 to 5 mol % not only decreased the reaction time from 6 to 4 h but also increased the product yield from 95% to 98%. This showed that the catalyst concentration plays a major role in the optimization of the product yield. The use of 10 mol % of CAN decreased the yield of the product to 67%. A possible explanation for the low product yield is that the starting material or the product may have been destroyed during the reaction when excess amount (10 mol %) of CAN was used in the reaction and thus 5 mol % CAN is the suitable choice for the optimum yield of N-substituted decahydroacridine-1,8-diones (Table 1).

The effect of temperature on reaction rate as well as on yields of products was also investigated. Faster reactions occurred on increasing the temperature but the product yield decreased at high temperature because one of the reactants oxidizes at high temperature in the presence of CAN (Table 1).

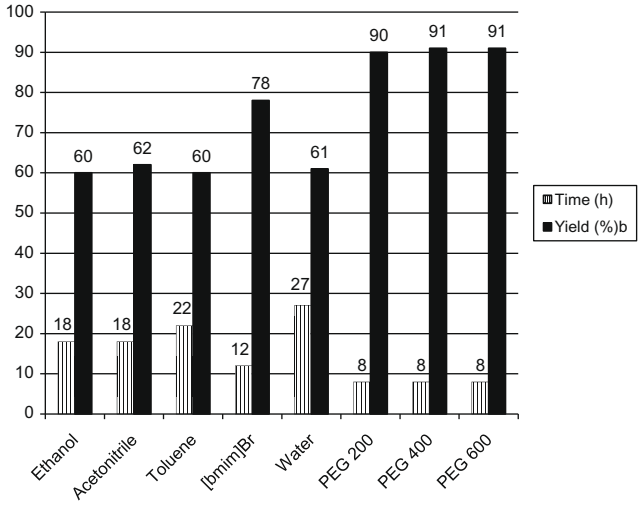

Figure 1. Synthesis of N-substituted decahydroacridine-1,8-diones in various solvents. Reaction conditions: cyclohexadione (2 mmol), benzaldehyde (1 mmol), aniline (1 mmol); temperature 50 °C. Isolated and unoptimized yields.

Table 1
Catalytic activity evaluation and effect of temperature for the synthesis of N-substituted decahydroacridine-1,8-diones[a]

Catalytic activity evaluation				Effect of temperature			
Entry	CAN (mol%)	Time (h)	Yield[b] (%)	Entry	Temperature (° C)	Time (h)	Yield[b] (%)
1	0	8	83	1	25	6	98
2	2	6	94	2	50	4	98
3	5	4	98	3	65	3.5	93
4	10	3	67	4	80	3	78

[a] Reaction conditions: cyclohexadione (2 mmol), benzaldehyde (1 mmol), aniline (1 mmol); solvent PEG 400.
[b] Isolated and unoptimized yields.

Table 2
Synthesis of various N-substituted decahydroacridine-1,8-diones using CAN and PEG[a]

Entry	R_1	R_2	R_3	R_4	Time (h)	Yield[b] (%)
4a	H	H	H	H	4	98
4b	H	H	$-4OCH_3$	H	4	96
4c	H	H	–4Cl	H	4	98
4d	H	H	$-3NO_2$	H	3.5	97
4e	H	H	H	–4Br	4	93
4f	H	H	H	$-CH_2C_6H_5$	4	98
4g	CH_3	CH_3	H	H	4	96
4h	CH_3	CH_3	$-4OCH_3$	H	4	96
4i	CH_3	CH_3	–4Cl	H	4	97
4j	CH_3	CH_3	$-3NO_2$	H	3.5	98
4k	CH_3	CH_3	H	–4Br	4	94
4l	CH_3	CH_3	H	$-CH_2C_6H_5$	4	97

[a] Reaction conditions: active methylene compound (2 mmol), aldehyde (1 mmol), aniline (1 mmol), CAN (5 mol %); solvent PEG 400; temperature 50 °C.
[b] Isolated and unoptimized yields.

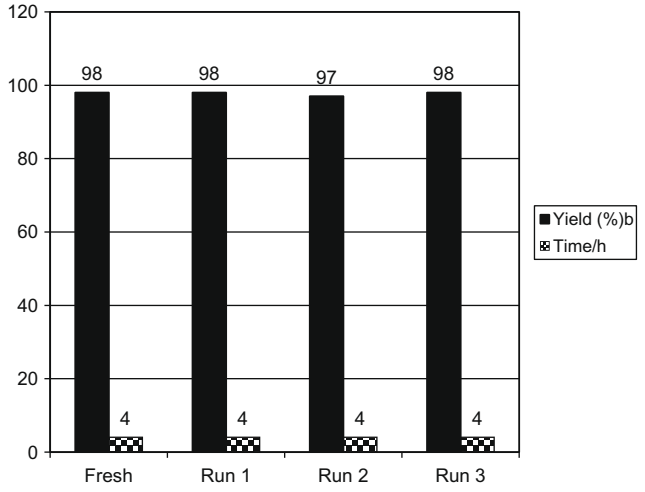

Figure 2. Recycling yields. Reaction conditions: cyclohexadione (2 mmol), benzaldehyde (1 mmol), aniline (1 mmol), CAN (5 mol %); solvent PEG 400. Isolated and unoptimized yields.

In order to extend the range of substrates, we intended to apply our methodology to a wide range of aldehydes and anilines in the presence of 5 mol % CAN under similar conditions.[22] As expected, satisfactory results were obtained for both electron-donating and electron-withdrawing groups (Table 2).

To check the ecofriendliness of PEG, we recycled PEG 400 for three times (Fig. 2). The reaction proceeded cleanly with consistent results, although a weight loss of ~5% of PEG 400 was observed from cycle to cycle due to mechanical loss.

3. Conclusion

In conclusion we have developed an effective catalytic system PEG 400/CAN for the synthesis of N-substituted decahydroacridine-1,8-diones. The methodology is simple, efficient, and environmentally friendly with simple work-up. We could reuse our solvent system several times. All these characteristics of our protocol make the reaction quite suitable for scale up and commercialization.

Acknowledgment

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22. *General procedure for the synthesis of N-substituted decahydroacridine-1,8-diones*: In a 50 ml round-bottomed flask, cyclohexadione (2 mmol), aromatic aldehyde (1 mmol), and aniline (1 mmol) in PEG (0.2 ml) were mixed and stirred at 50 °C. To this CAN (ceric ammonium nitrate) (5 mol %) was added. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was cooled with a dry ice-acetone bath to precipitate the PEG and was extracted with ether (PEG being insoluble in ether). The ether layer was decanted, dried, and concentrated under reduced pressure. The product though seen as a single compound by TLC was subjected to further purification by silica gel column chromatography using 20% ethyl acetate and 80% hexane as an eluent to yield the products **4**(**a–l**). The recovered PEG was reused for consecutive runs. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, ^{1}H NMR, mass spectral, and elemental analysis data). The spectral data for new products are listed.
9,10-Diphenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione(**4a**, $C_{25}H_{23}NO_2$): Mp = 274–276 °C (Lit. mp = 274–276 °C[18]).
9-(4-Methoxy-phenyl)-10-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4b**, $C_{26}H_{25}NO_3$): Mp = 270–272 °C (Lit. mp = 270–272 °C[19]).
9-(4-Chloro-phenyl)-10-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4c**, $C_{25}H_{22}ClNO_2$): Mp = 292–295 °C. IR (KBr): 1426 (C=C), 1593 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34–1.56 (m, 12H, CH_2), 5.32 (s, 1H), 6.97–7.56 (m, 9H, Ar). MS (EI): *m*/*z* calcd for $C_{25}H_{22}ClNO_2$: 403.13; found: 403.18. Anal. Calcd for $C_{25}H_{22}ClNO_2$: C, 74.34; H, 5.49; N, 3.47. Found: C, 74.28; H, 5.52; N, 3.43.
9-(3-Nitro-phenyl)-10-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4d**, $C_{25}H_{22}N_2O_4$): Mp = 278–280 °C. IR (KBr): 1435 (C=C), 1604 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87–1.32 (m, 12H, CH_2), 5.32 (s, 1H), 6.52–7.96 (m, 9H, Ar). MS (EI): *m*/*z* calcd for $C_{25}H_{22}N_2O_4$: 414.16; found: 414.27. Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76. Found: C, 72.37; H, 5.29; N, 6.72.
10-(4-Bromo-phenyl)-9-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4e**, $C_{25}H_{22}BrNO_2$): Mp = 264–267 °C. IR (KBr): 1442 (C=C), 1598 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99–1.34 (m, 12H, CH_2), 5.31 (s, 1H), 6.32–7.21 (m, 9H, Ar). MS (EI): *m*/*z* calcd for $C_{25}H_{22}BrNO_2$: 447.08; found: 447.26. Anal. Calcd for $C_{25}H_{22}BrNO_2$: C, 66.97; H, 4.95; N, 3.12. Found: C, 66.94; H, 4.89; N, 3.17.
10-Benzyl-9-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4f**, $C_{26}H_{25}NO_2$): Mp = 291–294 °C (Lit. mp = 291–294 °C[18]).
3,3,6,6-Tetramethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4g**, $C_{29}H_{31}NO_2$): Mp = 254–256 °C (Lit. mp = 254–256 °C[20]).
9-(4-Methoxy-phenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4h**, $C_{30}H_{33}NO_3$): Mp = 220–222 °C (Lit. mp = 220–222 °C[20]).
9-(4-Chloro-phenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4i**, $C_{29}H_{30}ClNO_2$): Mp = 244–246 °C (Lit. mp = 244–246 °C[21]).
3,3,6,6-Tetramethyl-9-(3-nitro-phenyl)-10-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4j**, $C_{24}H_{30}N_2O_4$): Mp = 297–299 °C. IR (KBr): 1436 (C=C), 1572 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (s, 12H, $4CH_3$), 1.92 (s, 4H, CH_2), 2.72 (s, 4H, CH_2), 5.31 (s, 1H), 6.32–8.63 (m, 9H, Ar). MS (EI): *m*/*z* calcd for $C_{24}H_{30}N_2O_4$: 470.56; found: 470.52. Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 74.02; H, 6.43; N, 5.95. Found: C, 74.08; H, 6.47; N, 5.89.
10-(4-Bromo-phenyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4k**, $C_{24}H_{30}BrNO_2$): Mp = 269–272 °C. IR (KBr): 1472

(C=C), 1598 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 12H, $4CH_3$), 1.97 (s, 4H, CH_2), 2.78 (s, 4H, CH_2), 5.30 (s, 1H), 6.32–7.21 (m, 9H, Ar). MS (EI): *m*/*z* calcd for $C_{24}H_{30}BrNO_2$: 503.15; found: 503.21. Anal. Calcd for $C_{24}H_{30}BrNO_2$: C, 69.05; H, 5.99; N, 2.78. Found: C, 69.11; H, 5.92; N, 2.75.

10-Benzyl-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (**4l**, $C_{30}H_{33}NO_2$): Mp = 301–303 °C. IR (KBr): 1483 (C=C), 1579 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 12H, $4CH_3$), 1.92 (s, 4H, CH_2), 2.73 (s, 4H, CH_2), 3.87 (s, 2H, CH_2), 5.29 (s, 1H), 7.02–7.19 (m, 10H, Ar). MS (EI): *m*/*z* calcd for $C_{30}H_{33}NO_2$: 439.25; found: 439.29. Anal. Calcd for $C_{30}H_{33}NO_2$: C, 81.97; H, 7.57; N, 3.19. Found: C, 81.88; H, 7.62; N, 3.12.