# Iron(III) phosphate-catalyzed synthesis of 7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-ones

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One-pot $FePO_4$-catalyzed three-component reaction of 1-naphthylamine, aldehydes, and cyclic 1,3-dicarbonyl compounds affords 7,10,11,12-tetrahydrobenzo[*c*]acridines in high yields.

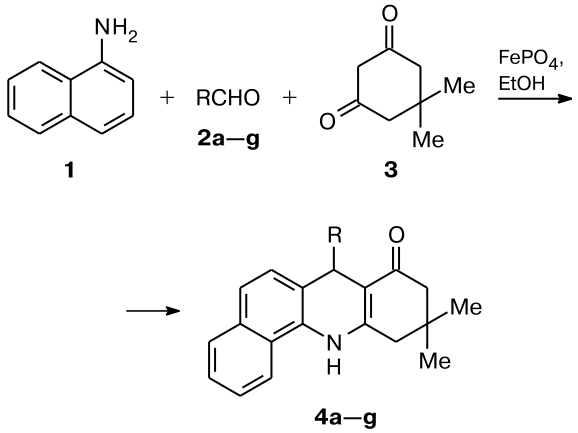
**Key words:** benzo[*c*]acridines, naphthylamine, aldehydes, one-pot reaction.

Lately, extensive research on the synthesis of tricyclic compounds containing acridine moieties has been reported. Acridine derivatives possess antitumor,[1] carcinogenic,[2] and anti-malaria activities,[3] and, therefore, they can be used for heart defibrillation.[4] Owing to its planar structure, acridine chromophore sometimes has excellent DNA binding properties. Recently, the synthesis of new polyacridines promising as bis-intercalating agents has been described.[5] Moreover, acridine skeleton fused with a five or six-membered ring yields polycyclic derivatives playing an important role as DNA-intercalating anticancer drugs.[6] Acridine derivatives are also of increasing interest due to the industrial production of synthetic fuels, that may contain nitrogen analogs of polycyclic aromatic hydrocarbons.[4] Thus, the synthesis of acridine derivatives is an important and principal task in modern organic chemistry.

Many methods are available for the preparation of benzoacridine derivatives: reactions of *N*-arylidene-1-naphthylamine with 1,3-dicarbonyl compounds in ethanol[7] or water using benzyltriethylammonium bromide as a catalyst[8,9] and three-component reactions of naphthylamine, dimedone, and aldehyde in ethanol carried out either on heating[10,11] or under microwave[12,13] and ultrasonic[14,15] irradiation.

These methods despite some merits have their shortcomings, such as low yield, high reaction temperature, and long reaction time. Herein we present a synthetic procedure to access dibenzo[*c*]acridine derivatives *via* $FePO_4$-catalyzed three-component reaction of 1-naphthylamine (**1**), aromatic aldehydes **2**, and dimedone **3** (Scheme 1) and a comparison of the efficiency of this procedure with known conventional methods.

**Scheme 1**




R = Ph (**a**), 4-$ClC_6H_4$ (**b**), 2,4-$Cl_2C_6H_3$ (**c**), 3,4-$(MeO)_2C_6H_3$ (**d**), 2-$MeC_6H_4$ (**e**), 3-$HOC_6H_4$ (**f**), CH=CHPh (**g**)

## Results and Discussion

To optimize the reaction conditions for the synthesis of dibenzo[*c*]acridines **4a**—**g**, the $FePO_4$-catalyzed three-component condensation of 1-naphthylamine (**1**), benzaldehyde (**2a**), and dimedone **3** was carried out in different solvents at room temperature. We examined the effect of the solvents (water, $CHCl_3$, MeCN, EtOH) on the yield of compound **4a** in this model reaction (Table 1). The highest yield of **4a** (90%) was achieved with EtOH as a solvent (see Table 1, entry *4*). When the reaction was

**Table 1.** Effect of different solvents on the yield of compound **4a***

| Entry | Solvent | Yield (%) |
|---|---|---|
| *1* | Water | 25 |
| *2* | $CHCl_3$ | 46 |
| *3* | MeCN | 63 |
| *4* | EtOH | 90 |

* Reaction time 1 h, temperature 20 °C.

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**Table 2.** One pot synthesis[a] of benzo[*c*]acridine derivatives **4a**—**g**

| Product | *t*/min | Yield (%) | M.p./°C |
|---|---|---|---|
| **4a** | 60 | 90 | 262—264[14] |
| **4b** | 60 | 85 | 269—271[14] |
| **4c** | 75 | 83 | 284—288[14] |
| **4d** | 90 | 95 | 253—259[13] |
| **4e** | 50 | 88 | 270—274[7] |
| **4f** | 90 | 90 | 187—195[b] |
| **4g** | 45 | 88 | 175—180[b] |

[a] Solvent EtOH, temperature 20 °C.
[b] Compounds **4f** and **4g** were first synthesized in the present work.

performed in water, $CHCl_3$, and MeCN (entries *1*—*3*), product **4a** was obtained in the yields from poor to moderate.

To generalize this reaction to a library synthesis, we extended it to various aldehydes (see Scheme 1) to synthesize the corresponding derivatives **4b**—**g**. As seen from Table 2, in all cases the yields were high. The described procedure is suitable for aromatic aldehydes bearing both electron-releasing and electron-withdrawing substituents in the benzene ring. The reaction proceeds with relatively high rate. However, it is worthy to note that the electron-withdrawing substituents favor the transformation. The described method towards benzo[*c*]acridine derivatives is convincingly superior to the reported methods[7,13,14] with respect to the yield, reaction time, simplicity, and safety.

To show the merits of this catalytic method in comparison with the previously reported protocols, we compared the yields of compound **4a** achieved under various conditions (Table 3). The advantages of our method are evident regarding the catalyst loading and easiness of catalyst separation, which are both very important in chemical industry.

In summary, we have developed a novel modified procedure to synthesize benzo[*c*]acridine derivatives in high yields. The advantages of this method are mild reaction conditions, easiness of the product isolation, availability of the starting compounds, and noticeable environmental benefits as compared with the known procedures.

## Experimental

Melting points were measured using the open capillary with an Electro Thermal 9200 apparatus. IR spectra were recorded on a Bruker FT-IR spectrometer in the KBr pellets with the scanning range of 4000—400 $cm^{-1}$. The products were identified by a comparison of their physicochemical and spectral data with those reported for the authentic samples. $^1H$ and $^{13}C$ NMR spectra were obtained on a Bruker DRX-500 instrument in $CD_3Cl$. Mass spectra were recorded on an Agilent 5973 Network Mass Selective Detector. Elemental analyses were performed on a Carlo Erba 106 Perkin—Elmer model 240 analyzer.

**7,10,11,12-Tetrahydrobenzo[*c*]acridin-8(9*H*)-ones 4a—g (general procedure).** A 50 ml-flask was charged with a mixture of 1-naphthylamine (1 mmol), dimedone (1 mmol), aldehyde (1 mmol), $FePO_4$ (10 mol.%), and EtOH (10 mL). The reaction mixture was stirred at 20 °C for the time given in Table 2. After completion of the reaction (TLC monitoring), the mixture was poured into ice-water (50 mL), the precipitate was collected by filtration. Recrystallization from EtOH gave pure product.

**10,10-Dimethyl-7-phenyl-7,10,11,12-tetrahydrobenzo[*c*]-acridin-8(9*H*)-one (4a).** White crystals, m.p. 262—264 °C. IR, ν/$cm^{-1}$: 3301 (NH); 2956, 2868 (CH aliph.); 1689 (C=O); 1595 (C=C arom.); 1072 (C—O). $^1H$ NMR, δ: 1.03, 1.08 (both s, 3 H each, $CH_3$); 2.05 (d, 1 H, CH, $J$ = 10.0 Hz); 2.07 (d, 1 H, CH, $J$ = 10.0 Hz); 2.58 (d, 1 H, CH, $J$ = 15.0 Hz); 2.61 (d, 1 H, CH, $J$ = 15.0 Hz); 5.82 (s, 1 H, CH); 6.87—7.07 (m, 9 H, ArH); 7.71 (d, 1 H, ArH, $J$ = 8.6 Hz); 8.45 (d, 1 H, ArH, $J$ = 8.5 Hz); 9.26 (s, 1 H, NH). MS, *m/z*: 353.46 $[M]^+$.

**7-(4-Chlorophenyl)-10,10-dimethy-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one (4b).** White crystals, m.p. 269—271 °C. IR, ν/$cm^{-1}$: 3530 (NH), 2950 (CH aliph.); 1630 (C=O); 1579 (C=C arom.); 1080 (C—O). $^1H$ NMR, δ: 0.99, 1.07 (both s, 3 H each, $CH_3$); 2.01 (d, 1 H, CH, $J$ = 10.0 Hz); 2.03 (d, 1 H,

**Table 3.** A comparison of different synthetic procedures to access compound **4a**

| Entry | Initiation | *m*/g | *t*/min | Solvent | Yield (%) |
|---|---|---|---|---|---|
| *1* | BNBTS | 0.10 | 32 | —[a] | 82[16] |
| *2* | NBS | 0.08 | 84 | —[a] | 84[16] |
| *3* | Ultrasound irradiation | —[b] | 120 | EtOH | 91[14] |
| *4* | MW/neutral aluminum oxide | —[b] | 9 | EtOH | 75[17] |
| *5* | MW/basic aluminum oxide | —[b] | 8.5 | EtOH | 80[17] |
| *6* | MW | —[b] | 2 | —[a] | 87[17] |
| *7* | $FePO_4$ | 0.022 | 60 | EtOH | 90[c] |

*Note*: *m* is the amount of catalyst used in the reaction; *t* is the reaction time; MW is microwave irradiation; BNBTS is *N*,*N*´-dibromo-*N*,*N*´-ethane-1,2-diylbis(4-toluenesulfonamide); NBS is *N*-bromosuccinimide.
[a] Reaction was carried out without solvent.
[b] Reaction was carried out without catalyst.
[c] Present work.

CH, $J$ = 10.0 Hz); 2.58 (d, 1 H, CH, $J$ = 15.0 Hz); 2.61 (d, 1 H, CH, $J$ = 15.0 Hz); 5.30 (s, 1 H, CH); 7.14—7.31 (m, 5 H, ArH); 7.45—7.59 (m, 2 H, ArH); 7.45—7.63 (m, 2 H, ArH); 8.43 (d, 1 H, ArH, $J$ = 8.7 Hz); 9.35 (s, 1 H, NH). MS, $m/z$: 387.9 $[M]^+$.

**7-(2,4-Dichlorophenyl)-10,10-dimethyl-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one (4c).** White crystals, m.p. 284—288 °C. IR, ν/cm$^{-1}$: 3306 (NH); 2956 (CH aliph.); 1684 (C=O); 1587 (C=C arom.); 1086 (C—O). $^1$H NMR, δ: 1.03, 1.08 (both s, 3 H each, $CH_3$); 2.03 (d, 1 H, CH, $J$ = 15.0 Hz); 2.06 (d, 1 H, CH, $J$ = 15.0 Hz); 2.65 (d, 1 H, CH, $J$ = 10.0 Hz); 2.67 (d, 1 H, CH, $J$ = 10.0 Hz); 5.71 (s, 1 H, CH); 7.14—7.37 (m, 7 H, ArH); 7.82 (d, 1 H, ArH, $J$ = 8.1 Hz); 8.48 (d, 1 H, ArH, $J$ = 8.1 Hz); 9.29 (s, 1 H, NH). MS, $m/z$: 422.35 $[M]^+$.

**7-(3,4-Dimethoxyphenyl)-10,10-dimethyl-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one (4d).** White crystals, m.p. 253—259 °C. IR, ν/cm$^{-1}$: 3368 (NH); 2955 (CH aliph.); 1597 (C=C arom.); 1026 (C—O). $^1$H NMR, δ: 1.03, 1.08 (both s, 3 H each, $CH_3$); 2.05 (d, 1 H, CH, $J$ = 15.0 Hz); 2.08 (d, 1 H, CH, $J$ = 15.0 Hz); 2.65 (d, 1 H, CH, $J$ = 10.0 Hz); 2.67 (d, 1 H, CH, $J$ = 10.0 Hz); 3.65, 3.68 (both s, 3 H each, $OCH_3$); 5.17 (s, 1 H, $CH_3$); 6.56—6.78 (m, 2 H, ArH); 6.81 (s, 1 H, ArH); 7.35 (d, 1 H, ArH, $J$ = 8.5 Hz); 7.61—7.63 (m, 3 H, ArH); 8.15 (d, 1 H, ArH, $J$ = 8.4 Hz); 9.27 (s, 1 H, NH). MS, $m/z$: 413.51 $[M]^+$.

**10,10-Dimethyl-7-(2-methylphenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one (4e).** White crystals, m.p. 167—170 °C. IR, ν/cm$^{-1}$: 3290 (NH); 2955, 2834 (CH aliph.); 1688 (C=O); 1591 (C=C); 1028 (C—O). $^1$H NMR, δ: 1.02, 1.09 (both s, 3 H each, $CH_3$); 2.06 (d, 1 H, CH, $J$ = 10.0 Hz); 2.08 (d, 1 H, CH, $J$ = 10.0 Hz); 2.57 (d, 1 H, CH, $J$ = 15.0 Hz); 2.58 (d, 1 H, CH, $J$ = 15.0 Hz); 2.7 (s, 3 H, $CH_3$); 5.82 (s, 1 H, CH); 6.79—7.01 (m, 8 H, ArH); 7.86 (d, 1 H, ArH, $J$ = 8.0 Hz); 8.45 (d, 1 H, ArH, $J$ = 8.4 Hz); 9.26 (s, 1 H, NH). MS, $m/z$: 367.48 $[M]^+$.

**7-(3-Hydroxyphenyl)-10,10-dimethyl-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one (4f).** White crystals, m.p. 187—195 °C. IR, ν/cm$^{-1}$: 3314 (NH); 3070 (C—H aliph.); 2956 (CH aliph.); 1640 (C=O); 1468 (C=C arom.); 1047 (C—O). $^1$H NMR, δ: 0.95, 1.07 (both s, 3 H each, $CH_3$); 2.06 (d, 1 H, CH, $J$ = 10.5 Hz); 2.17 (d, 1 H, CH, $J$ = 10.5 Hz); 2.52 (d, 1 H, CH, $J$ = 15.5 Hz); 2.64 (d, 1 H, CH, $J$ = 15.5 Hz); 5.75 (s, 1 H, CH); 6.80 (d, 1 H, ArH, $J$ = 10.0 Hz); 6.93—7.01 (m, 3 H, ArH); 7.13 (d, 2 H, ArH, $J$ = 5.0 Hz); 7.31 (s, 1 H, ArH); 7.36—7.53 (m, 1 H, ArH); 7.69 (d, 1 H, ArH, $J$ = 10.0 Hz); 7.75 (s, 1 H, NH); 7.85 (d, 1 H, ArH, $J$ = 10.0 Hz); 8.95 (s, 1 H, OH). MS, $m/z$: 369.46 $[M]^+$. Found (%): C, 81.21; H, 6.22; N, 3.71. $C_{25}H_{23}NO_2$. Calculated (%): C, 81.27; H, 6.27; N, 3.79.

**10,10-Dimethyl-7-(2-phenylethenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one (4g).** Yellow crystals, m.p. 175—180 °C. IR, ν/cm$^{-1}$: 3342 (NH); 2956 (CH aliph.); 1635 (C=O); 1590, 1557 (C=C arom. and aliph.). $^1$H NMR, δ: 1.11, 1.16 (both s, 3 H each, $CH_3$); 2.16 (d, 1 H, CH, $J$ = 10.5 Hz); 2.7 (d, 1 H, CH, $J$ = 10.5 Hz); 2.34 (d, 1 H, CH, $J$ = 15.5 Hz); 2.35 (d, 1 H, CH, $J$ = 15.5 Hz); 5.06 (d, 1 H, CH, $J$ = 5.0 Hz); 6.30 (d, 1 H, CH, $J$ = 15.0 Hz); 6.36 (dd, 1 H, CH, $J$ = 15.0 Hz, $J$ = 5.0 Hz); 6.90 (s, 1 H, NH); 7.16—7.22 (m, 5 H, ArH); 7.32 (d, 2 H, ArH, $J$ = 5.0 Hz); 7.55 (m, 2 H, ArH); 7.77 (d, 1 H, ArH, $J$ = 10.0 Hz); 7.85 (d, 1 H, ArH, $J$ = 10.0 Hz). MS, $m/z$: 379.49 $[M]^+$. Found (%): C, 85.39; H, 6.58; N, 3.57. $C_{27}H_{25}NO$. Calculated (%): C, 85.45; H, 6.64; N, 3.69.

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