JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

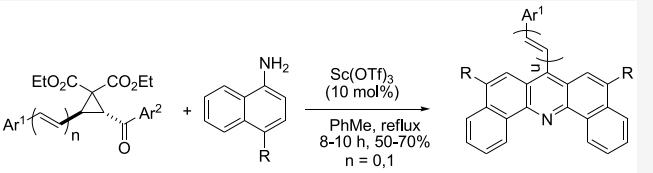
# Scandium(III) Triflate-Catalyzed Reaction of Aroyl-Substituted Donor−Acceptor Cyclopropanes with 1-Naphthylamines: Access to Dibenzo[*c*,*h*]acridines

Murugesan Thangamani and Kannupal Srinivasan*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c02105 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** The reaction of aroyl-substituted donor−acceptor (D−A) cyclopropanes with two equivalents of 1-naphthylamines in the presence of a catalytic amount of scandium(III) triflate provides access to dibenzo[*c*,*h*]acridines. The key steps of the transformation are the formation of nucleophilic ring-opening products from the D−A cyclopropanes and 1-naphthylamines and their subsequent fragmentation and cyclization. The method has a reasonable substrate scope, and the products are formed in 50−70% yields.






Donor−acceptor (D−A) cyclopropanes are renowned building blocks in organic synthesis, which could be ingeniously exploited for the synthesis of various carbocyclic, heterocyclic, and acyclic compounds.[1] They usually undergo three types of reactions, namely, annulation, ring opening, and ring expansion reactions. Among those reactions, their ring-opening reactions with *N*-nucleophiles serve as versatile tools for the access of a variety of *N*-containing cyclic and acyclic products.[1d,2]

Acridines are one of the important heterocyclic compounds that have received huge attention, owing to their assortment of applications in various fields. The acridine motif is found in a large number of bioactive natural products such as cytotoxic *cystodytins A*−*K*, neurogenin2 promoting *insubosins A*−*C*, and antibacterial *xanthacridone*.[3] Many acridine derivatives also display a wide range of pharmaceutical activities, and some of them, such as *amsacrine*, *pyronaridine*, and *quinacrine*, serve as antineoplastic, antimalarial, and antiprotozoal drugs, respectively.[4] Many acridine derivatives also find application as photocatalysts,[5] functional materials,[6] and fluorescent dyes to study cellular processes.[7] The significance of acridine derivatives has acted as a stimulus for the development of numerous methods for their synthesis,[8] in addition to classical methods.[9]

Among various acridines, dibenzo[*c*,*h*]acridines exhibit unique photophysical properties, and hence, they are considered promising OLED materials.[10] Despite their importance, only sporadic reports are available for the synthesis of dibenzo[*c*,*h*]acridines in the literature, and they often involve multistep procedures.[10,11] So alternate strategies for the access of dibenzo[*c*,*h*]acridines are necessary. Recently, Langer and co-workers have developed a convenient procedure for the access of dibenzo[*c*,*h*]acridines through methanesulfonic acid-mediated electrophilic cycloisomerization of 2,6-diaryl-3,5-diynylpyridines.[12]

Our research group is interested in exploring the synthetic potentials of *trans*-2-aroyl-3-arylcyclopropane-1,1-dicarboxylates **1** (Scheme 1; also termed as aroyl-substituted D−A cyclopropanes).[13] Recently, we reported the ring-opening reactions of **1** with hydrazines for the access of dihydropyrazoles **2** and cyclopropane-fused pyridazinones **3** [Scheme 1a].[13d] In continuation of the work, we became interested in studying their ring-opening reactions with various amines with a view to obtain useful nitrogen-containing compounds. Although many of those reactions gave complicated mixtures (with amines such as aniline, 2-, 3-, or 4-methylaniline and 2-naphthylamine), we found that the scandium(III) triflate-catalyzed reaction of the cyclopropane dicarboxylates **1** and also related *trans*-2-aroyl-3-styrylcyclopropane-1,1-dicarboxylates **4** with 1-naphthylamines **5** provide access to various dibenzo[*c*,*h*]acridines **6** [Scheme 1b]. We believe that the unexpected formation of the products coupled with the availability of only limited methods for the synthesis of such compounds compensates for the lack of atom economy in the reaction. It may also be noted that arylamine acting as a C-nucleophile for the ring opening of D−A cyclopropanes is rare in the literature.[2e]

We began the study by taking the reaction of cyclopropane dicarboxylate **1a** with 1-naphthylamine (**5a**) as a model reaction to identify optimal reaction conditions (Table 1).

**Received:** September 1, 2020

**Scheme 1. Ring-Opening Reactions of Aroyl-Substituted D−A Cyclopropanes with (a) Hydrazines and (b) 1-Naphthylamines**

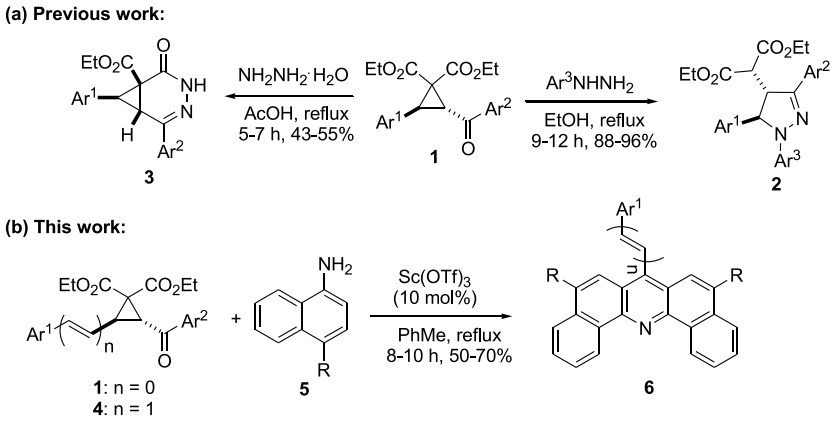
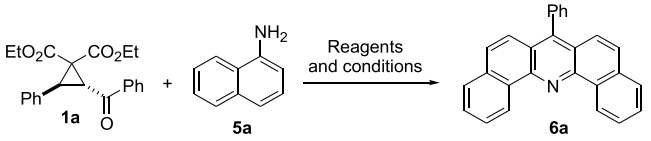



**Table 1. Optimization of the Reaction Conditions**



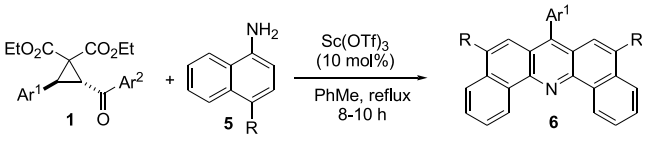

| S. No. | reagents and conditions | yield of **6a** (%)[a] |
|---|---|---|
| 1 | **5a** (1 equiv), $Sc(OTf)_3$ (10 mol %), DCM, rt or reflux, 24 h | NR[b] |
| 2 | **5a** (1 equiv), $Sc(OTf)_3$ (10 mol %), 1,2-DCE, rt or reflux, 24 h | NR[b] |
| 3 | **5a** (1 equiv), $Sc(OTf)_3$ (10 mol %), PhMe, rt, 24 h | NR[b] |
| 4 | **5a** (1 equiv), $Sc(OTf)_3$ (10 mol %), PhMe, reflux, 12 h | 30 |
| 5 | **5a** (2 equiv), $Sc(OTf)_3$ (10 mol %), PhMe, reflux, 10 h | 68 |
| 6 | **5a** (3 equiv), $Sc(OTf)_3$ (10 mol %), PhMe, reflux, 10 h | 66 |
| 7 | **5a** (2 equiv), $Sc(OTf)_3$ (10 mol %), PhMe, 80 °C, 12 h | 55 |
| 8 | **5a** (2 equiv), $Sc(OTf)_3$ (5 mol %), PhMe, reflux, 10 h | 40 |
| 9 | **5a** (2 equiv), $Sc(OTf)_3$ (20 mol %), PhMe, reflux, 10 h | 52 |
| 10 | **5a** (2 equiv), $AlCl_3$, $SnCl_4$ or $BF_3{\cdot}OEt_2$ (10 mol % or 1 equiv), PhMe, reflux, 12 h | NR[b] |
| 11 | **5a** (2 equiv), $Cu(OTf)_2$, $In(OTf)_3$, $Yb(OTf)_3$ or *p*-TsOH (10 mol %), PhMe, reflux, 12 h | NR[b] |
| 12 | **5a** (2 equiv), $Sc(OTf)_3$ (10 mol %), THF, EtOH or $MeNO_2$, reflux, 12 h | NR[b] |

[a]Isolated yield. [b]No reaction.

Initially, we selected scandium(III) triflate as a catalyst for the reaction, owing to its tendency of weakly coordinating with amines[14] and also its widespread use in D−A cyclopropane chemistry.[1] When the reaction was conducted in the presence of 10 mol % of scandium(III) triflate using DCM or 1,2-DCE as a solvent, the reactions did not materialize at room temperature as well as under refluxing conditions (Table 1, entries 1 and 2). When toluene was used as a solvent, the reaction did not take place even after 24 h at room temperature (entry 3). However, the reaction afforded dibenzo[*c*,*h*]acridine **6a** in 30% yield when heated under reflux for 12 h (entry 4) (the structure of **6a** was confirmed by X-ray crystallographic analysis[15]). The yield of **6a** increased to 68% when 2 equiv of **5a** was used in the reaction (entry 5). However, the use of 3 equiv of **5a** did not alter the yield of **6a** significantly (entry 6). When the temperature of the reaction (using two equivalents of **5a**) was reduced to 80 °C, the yield of **6a** was also reduced to 55% (entry 7). When the amount of catalyst in the reaction was reduced to 5 mol %, the yield of **6a** decreased to 40% (entry 8). At the same time, increasing the amount of catalyst to 20 mol % decreased the yield of **6a** to 52% due to the formation of more impurities (entry 9). The reaction did not take place when a catalytic or stoichiometric amount of $AlCl_3$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ was used as Lewis acids, possibly due to the strong coordination of these Lewis acids to 1-naphthylamine (**6a**) (entry 10). Other triflate catalysts, such as copper(II) triflate, indium(III) triflate, and ytterbium(III) triflate and a Bronsted acid, *p*-TsOH, were ineffective for catalyzing the reaction (entry 11). Further, the reaction did not take place in other solvents such as THF, EtOH, and nitromethane (entry 12). So, we selected heating 1 equiv of cyclopropane dicarboxylate **1a** with 2 equiv of 1-naphthylamine (**5a**) in toluene under reflux as optimal conditions for the formation of dibenzo[*c*,*h*]acridine **6a**.

Adapting the optimized reaction conditions, we first probed the scope of the reaction for various *trans*-2-aroyl-3-arylcyclopropane-1,1-dicarboxylates and 1-naphthylamines (Table 2). Since the aroyl group of the cyclopropane is lost during the course of the reaction, we observed that both cyclopropane dicarboxylates **1a** ($Ar^1$ = $Ar^2$ = Ph) and **1b** ($Ar^1$ = Ph and $Ar^2$ = 4-$MeC_6H_4$) gave the same dibenzo[*c*,*h*]-

**Table 2. Scope of the Reaction for Various *trans*-2-Aroyl-3-arylcyclopropane-1,1-dicarboxylates and 1-Naphthylamines**




| entry | $Ar^1$, $Ar^2$ | R | yield of **6** (%)[a] |
|---|---|---|---|
| 1 | Ph, Ph (**1a**)[b] | H (**5a**) | 68 (**6a**) |
| 2 | Ph, 4-$MeC_6H_4$ (**1b**) | H (**5a**) | 62 (**6a**) |
| 3 | 4-$MeC_6H_4$, Ph (**1c**) | H (**5a**) | 70 (**6b**) |
| 4 | 4-$MeOC_6H_4$, Ph (**1d**) | H (**5a**) | 66 (**6c**) |
| 5 | 4-$ClC_6H_4$, Ph (**1e**) | H (**5a**) | 63 (**6d**) |
| 6 | 4-$O_2NC_6H_4$, Ph (**1f**) | H (**5a**) | *c* |
| 7 | 1-Naphthyl, Ph (**1g**) | H (**5a**) | 60 (**6e**) |
| 8 | Ph, Ph (**1a**) | Br (**5b**) | 66 (**6f**) |
| 9 | 4-$MeC_6H_4$, Ph (**1c**) | Br (**5b**) | 62 (**6g**) |
| 10 | 4-$NO_2C_6H_4$, Ph (**1f**) | Br (**5b**) | 50 (**6h**) |
| 11 | Ph, Ph (**1a**) | $NO_2$ (**5c**) | 52 (**6i**) |

[a]Isolated yield. [b]*cis*-Isomer of **1a** also forms **6a** in 63% yield. [c]Could not be isolated in pure form.

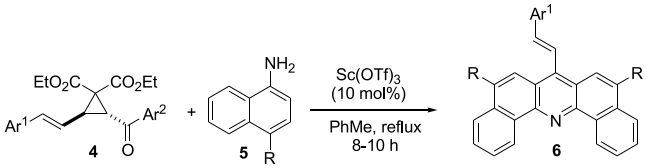


https://dx.doi.org/10.1021/acs.joc.0c02105
J. Org. Chem. XXXX, XXX, XXX−XXX

acridine **6a** with 1-naphthylamine (**5a**) (Table 2, entries 1 and 2). So we decided to vary only the $Ar^1$ ring of the cyclopropanes for further experiments. The reaction tolerates cyclopropane dicarboxylates **1c−e** having electron-donating and halogen-containing aryl rings such as *p*-tolyl, *p*-anisyl, and *p*-chlorophenyl rings as $Ar^1$and the respective dibenzo[*c*,*h*]-acridines **6b−d** are produced in 63−70% yields (entries 3−5). Although the reaction took place when the *p*-nitrophenyl ring was used as $Ar^1$, the respective dibenzo[*c*,*h*]acridine could not be isolated in pure form (entry 6). When cyclopropane dicarboxylate **1g** possessing bulky 1-naphthyl ring as $Ar^1$ was used, the reaction afforded the corresponding dibenzo[*c*,*h*]-acridine **6e** in 60% yield (entry 7). We also reacted cyclopropane dicarboxylates **1a**, **1c**, and **1f** with 4-bromo-1-naphthylamine (**5b**) and obtained the respective dibenzo[*c*,*h*]-acridines **6f−h** in 50−66% yields (entries 8−10). It is interesting to note that the presence of bromo substituents in the products **6f−h** would allow further synthetic elaboration through palladium chemistry. We also tested the reaction of cyclopropane dicarboxylate **1a** with 4-nitro-1-naphthylamine (**5c**), and the reaction also afforded the corresponding dibenzo[*c*,*h*]acridine **6i** in 52% yield (entry 11).

Next, we extended the scope of the reaction to another type of aroyl-substituted D−A cyclopropanes **4**, having the styryl moiety as a donor group, in order to see whether the presence of a vinyl unit has any effect on the outcome of the reaction (Table 3). Nevertheless, these styrylcyclopropane dicarboxylates **4** also exhibited a similar pattern of reactivity as their sister substrates. Thus, cyclopropane dicarboxylates **4a−d** having phenyl, *p*-anisyl, 2-thienyl, and 1-naphthyl rings attached to the vinyl unit gave the expected dibenzo[*c*,*h*]-acridines **6j−p** in 60−70% yields upon reaction with 1-naphthylamine (**5a**), 4-bromo-1-naphthylamine (**5b**), and 4-nitro-1-naphthylamine (**5c**) (entries 1−7).

**Table 3. Scope of the Reaction for Various *trans*-2-Aroyl-3-styrylcyclopropane-1,1-dicarboxylates and 1-Naphthylamines**




| entry | $Ar^1$, $Ar^2$ | R | yield of **6** (%)[a] |
|---|---|---|---|
| 1 | Ph, Ph (**4a**) | H (**5a**) | 70 (**6j**) |
| 2 | 4-$MeOC_6H_4$, Ph (**4b**) | H (**5a**) | 60 (**6k**) |
| 3 | 2-Thienyl, Ph (**4c**) | H (**5a**) | 62 (**6l**) |
| 4 | Ph, Ph (**4a**) | Br (**5b**) | 60 (**6m**) |
| 5 | 2-Naphthyl, Ph (**4d**) | Br (**5b**) | 66 (**6n**) |
| 6 | 2-Thienyl, Ph (**4c**) | Br (**5b**) | 60 (**6o**) |
| 7 | Ph, Ph (**4a**) | $NO_2$ (**5c**) | 61 (**6p**) |

[a]Isolated yield.

We have previously reported that diethyl *trans*-2-benzoyl-3-styrylcyclopropane-1,1-dicarboxylate **4a** when treated with $BF_3{\cdot}OEt_2$ in DCM undergoes ring opening to give the corresponding putative 1,3-zwitterionic intermediate, which captures $H_2O$ (from moisture) and undergoes fragmentation to yield cinnamaldehyde and phenacyl malonate (**7**).[13e] We have also observed that diethyl *trans*-2-benzoyl-3-phenyl-cyclopropane-1,1-dicarboxylate **1a** also undergoes similar fragmentation with $BF_3{\cdot}OEt_2$ to yield benzaldehyde and phenacyl malonate (**7**). So, we infer that a similar fragmentation is possible in the present transformation as well when the putative 1,3-zwitterionic intermediate from the cyclopropane captures the nucleophile (1-naphthylamine).[16] The absence of aroyl and diester moieties in the products also supports this point. Accordingly, we propose a plausible mechanism outlined in Scheme 2 for the formation of dibenzo[*c*,*h*]acridines in the present reactions, by taking the reaction between **1a** and **2a** as a representative example. In the presence of $Sc(OTf)_3$ (LA), 1-naphthylamine (**5a**) acts as a C-nucleophile and attacks the cyclopropane dicrboxylate **1a** at the carbon bearing the donor group to give intermediate **A**, which upon rearomatization produces the adduct **B**. The adduct **B** then undergoes fragmentation to form the intermediate **C** by eliminating phenacyl malonate (**7**). The intermediate **C** is further attacked by another molecule of 1-naphthylamine (**5a**), resulting in intermediate **D**. The electrocyclic ring closure of **D** with a loss of ammonia gives intermediate **E**, which finally undergoes aromatization with a loss of hydrogen to afford dibenzo[*c*,*h*]acridine **6a**. It may be noted that we are not able to isolate the eliminated phenacyl malonate (**7**) from the reaction mixture, possibly due to its untraceable reaction with 1-naphthylamine (**5a**). It is also noteworthy that the reaction of benzaldehyde or 1,3-dioxolane-protected benzaldehyde with **5a** does not give any trace of dibenzo[*c*,*h*]acridine **6a** under the current reaction conditions.

In summary, we have synthesized a series of dibenzo[*c*,*h*]-acridines through the scandium(III) triflate-catalyzed reaction of aroyl-substituted D−A cyclopropanes with 1-naphthyl-amines. The reaction proceeds through the ring opening of cyclopropane, the addition of naphthylamine, fragmentation of resulting intermediate, and subsequent cyclization. Given the limited methods available for the access of dibenzo[*c*,*h*]-acridines, the current method is a valuable addition to the existing methods.

## EXPERIMENTAL SECTION

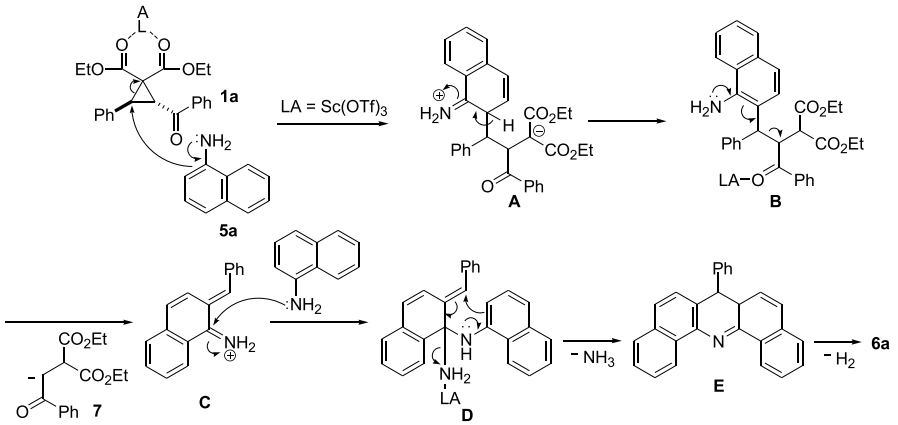
**General Remarks.** Melting points were determined by the open capillary tube method and are uncorrected. The $^1H$ and $^{13}C$ NMR spectra were recorded on a 400 MHz NMR spectrometer. High-resolution mass spectra (ESI) were recorded on a Q-Tof mass spectrometer. Low-resolution mass spectra (ESI) were recorded on an LC−MS spectrometer. Elemental analyses were performed on a CHN analyzer. X-ray crystallographic data were collected on a CCD diffractometer using graphite-monochromated Mo K$\alpha$ radiation. Thin-layer chromatography (TLC) was performed on precoated alumina sheets and detected under UV light. Silica gel (100−200 mesh) was used for column chromatography. The starting materials, *trans*-2-aroyl-3-aryl/styrylcyclopropane-1,1-dicarboxylates **1** and **4**, were prepared as per our earlier reports.[13b,e]

**General Procedure for the Synthesis of Acridines 6a−p.** To a solution of *trans*-2-aroyl-3-aryl/styryl-cyclopropane-1,1-dicarboxylate **1**/**4** (1.0 mmol) in toluene (5 mL) were added 1-naphthylamine **2** (2.0 mmol) and $Sc(OTf)_3$ (49 mg, 10 mol %), and the reaction mixture was heated in an oil bath under reflux for 8−10 h. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated under a vacuum. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1:9) as the eluent to give pure acridine **6**.

*7-Phenyldibenzo[c,h]acridine (**6a**).*[8a] Yellow solid. Yield: 241 mg (68%). Mp: 208−212 °C. $R_f$: 0.65 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.82 (d, $J$ = 8.0 Hz, 2H), 7.90−7.83 (m,


https://dx.doi.org/10.1021/acs.joc.0c02105
J. Org. Chem. XXXX, XXX, XXX−XXX

**Scheme 2. Mechanism for the Formation of Dibenzo[*c,h*]acridines (LA Coordination to Malonate Moiety Is Not Shown in Intermediate Structures for Clarity)**




4H), 7.77−7.23 (m, 2H), 7.68−7.59 (m, 5H), 754−7.52 (m, 2H), 7.48−7.46 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 145.8, 145.5, 136.6, 133.5, 132.1, 130.6, 128.7, 128.6, 128.2, 127.8, 127.4, 127.2, 125.5, 124.0, 123.7 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{18}N$, 356.1434; found, 356.1440.

*7-(p-Tolyl)dibenzo[c,h]acridine* (**6b**). Pale yellow solid. Yield: 258 mg (70%). Mp: 210−214 °C. $R_f$: 0.42 (EtOAc/hexane, 1:19 *v/v*). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.82 (d, *J* = 8.4 Hz, 2H), 7.90−7.82 (m, 4H), 7.76−7.72 (m, 2H), 7.68−7.65 (m, 2H), 7.58−7.56 (m, 2H), 7.44−7.42 (m, 2H), 7.36−7.35 (m, 2H), 2.54 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 146.0, 145.5, 138.0, 133.6, 133.5, 132.1, 130.5, 129.2, 128.7, 127.7, 127.2, 127.1, 125.5, 124.2, 123.8, 21.5 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{20}N$, 370.1590; found, 370.1597.

*7-(4-Methoxyphenyl)dibenzo[c,h]acridine* (**6c**).[8a] Pale yellow solid. Yield: 254 mg (66%). Mp: 209−211 °C. $R_f$: 0.44 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.48 (d, *J* = 8.0 Hz, 1H), 8.30 (d, *J* = 8.8 Hz, 3H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.89−7.82 (m, 3H), 8.00−7.65 (m, 6H), 7.07 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 160.8, 155.2, 146.2, 136.5, 133.9, 132.5, 128.9, 128.1, 127.8, 127.0, 126.8, 125.2, 124.7, 118.3, 114.2, 55.5 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{20}NO$, 386.1539; found, 386.1545.

*7-(4-Chlorophenyl)dibenzo[c,h]acridine* (**6d**). Yellow solid. Yield: 245 mg (63%). Mp: 214−216 °C. $R_f$: 0.50 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.81 (d, *J* = 8.4 Hz, 2H), 7.89−7.84 (m, 6H), 7.67−7.59 (m, 4H), 7.53−7.51 (m, 2H), 7.47−7.46 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 145.5, 144.3, 135.0, 134.4, 133.5, 131.99, 131.96, 128.9, 128.8, 127.8, 127.7, 127.3, 125.5, 123.6, 123.5 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{17}ClN$, 390.1044; found, 390.1048.

*7-(Naphthalen-1-yl)dibenzo[c,h]acridine* (**6e**). Yellow solid. Yield: 243 mg (60%). Mp: 210−214 °C. $R_f$: 0.48 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.88 (d, *J* = 8.0 Hz, 2H), 8.10−8.01 (m, 2H), 7.88−7.84 (m, 4H), 7.76−7.68 (m, 3H), 7.57−7.42 (m, 5H), 7.28−7.19 (m, 2H), 7.11−7.09 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 145.6, 144.2, 134.3, 133.7, 133.6, 132.7, 132.1, 128.83, 128.76, 128.5, 128.4, 127.9, 127.6, 126.7, 126.3, 126.2, 125.5, 125.47, 124.7, 124.1 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{20}N$, 406.1590; found, 406.1599.

*5,9-Dibromo-7-phenyldibenzo[c,h]acridine* (**6f**). Brown liquid. Yield: 339 mg (66%). $R_f$: 0.62 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.46−9.42 (m, 1H), 9.09−9.06 (m, 1H), 8.19−7.76 (m, 3H), 7.62−7.57 (m, 4H), 7.52−7.30 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 148.6, 147.9, 138.3, 137.7 133.4, 132.7, 131.8, 129.6, 128.9, 128.6, 128.0, 127.4, 126.6, 124.9, 123.0 ppm. MS (ESI) *m/z*: 533.37 $[M + Na]^+$. Anal. Calcd for $C_{27}H_{15}Br_2N$: C, 63.19; H, 2.95; N, 2.73. Found: C, 63.43; H, 2.97; N, 2.69.

*5,9-Dibromo-7-(p-tolyl)dibenzo[c,h]acridine* (**6g**). Yellow liquid. Yield: 327 mg (62%). $R_f$: 0.56 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.88 (d, *J* = 8.0 Hz, 2H), 7.96−7.88 (m, 2H), 7.82−7.80 (m, 2H), 7.74−7.71 (m, 2H), 7.64−7.61 (m, 2H), 7.50−7.48 (m, 2H), 7.42−7.40 (m, 2H), 2.60 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 146.0, 145.5, 138.0, 133.6, 132.1, 130.5, 129.2, 128.7, 127.7, 127.2, 127.1, 125.5, 124.2, 123.8, 21.5 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{18}Br_2N$, 525.9800; found, 525.9797.

*5,9-Dibromo-7-(4-nitrophenyl)dibenzo[c,h]acridine* (**6h**). Pale yellow liquid. Yield: 279 mg (50%). $R_f$: 0.18 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.78−9.68 (m, 2H), 8.26−8.24 (m, 1H), 7.82−7.68 (m, 5H), 7.61−7.54 (m, 3H), 7.43−7.37 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 145.1, 144.7, 135.9, 133.6, 133.0, 132.0, 130.5, 128.8, 127.9, 127.5, 125.7, 125.5, 124.0, 123.9, 122.6 ppm. MS (ESI) *m/z*: 573.43 $[M + NH_4]^+$. Anal. Calcd for $C_{27}H_{14}Br_2N_2O_2$: C, 58.09; H, 2.53; N, 5.02. Found: C, 58.33; H, 2.60; N, 5.10.

*5,9-Dinitro-7-phenyldibenzo[c,h]acridine* (**6i**). Pale yellow solid. Yield: 232 mg (52%). Mp: 217−219 °C. $R_f$: 0.16 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): 8.84 (d, *J* = 2.4 Hz, 2H), 8.55−8.43 (m, 2H), 8.33−8.25 (m, 6H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.63−7.58 (m, 4H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): 160.7, 150.4, 145.2, 138.52, 138.46, 131.4, 130.5, 129.1, 127.9, 125.9, 124.4, 123.2, 120.7 ppm. MS (ESI) *m/z*: 481.26 $[M + 2H_2O]^+$. Anal. Calcd for $C_{27}H_{15}N_3O_4$: C, 72.80; H, 3.39; N, 9.43. Found: C, 72.94; H, 3.44; N, 9.40.

*(E)-7-Styryldibenzo[c,h]acridine* (**6j**). Dark brown liquid. Yield: 267 mg (70%). [Yield: 756 mg (66%) on 3.0 mmol scale]. $R_f$: 0.80 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.50−9.48 (m, 1H), 8.34−8.33 (m, 2H), 8.19−8.17 (m, 1H), 8.09−7.88 (m, 3H), 7.78−7.70 (m, 7H), 7.69−7.45 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 155.5, 146.3, 139.8, 136.6, 133.9, 131.9, 129.3, 128.9, 128.2, 127.9, 127.53, 127.50, 127.0, 125.21, 125.16, 124.8, 118.9 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{20}N$, 382.1590; found, 382.1604.

*(E)-7-(4-Methoxystyryl)dibenzo[c,h]acridine* (**6k**). Brown liquid. Yield: 247 mg (60%). $R_f$: 0.63 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.44 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 15.2 Hz, 1H), 7.88−7.50 (m, 8H), 7.40−7.33 (m, 5H), 7.31−7.21 (m, 3H), 4.33 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 152.7, 144.9, 139.7, 137.1, 135.1, 133.7, 132.3, 128.9, 128.82, 128.77, 128.0, 127.9, 127.5, 126.7, 125.6, 125.1, 124.6, 38.6 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{22}NO$, 412.1696; found, 412.1692.

*(E)-7-[2-(Thien-2-yl)vinyl]dibenzo[c,h]acridine* (**6l**). Brown liquid. Yield: 239 mg (62%). $R_f$: 0.53 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.78 (d, *J* = 8.0 Hz, 1H), 7.84−7.65 (m, 6H), 7.41−7.35 (m, 4H), 7.28−7.21 (m, 4H), 6.68−6.66 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 148.2, 147.2, 140.7, 139.3, 133.4, 131.7, 128.8, 128.5, 128.1, 127.9, 127.7, 127.4, 127.2, 125.0,


https://dx.doi.org/10.1021/acs.joc.0c02105
J. Org. Chem. XXXX, XXX, XXX−XXX

124.3, 122.8, 122.7 ppm. HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{27}H_{18}NS$, 388.1154; found, 388.1153.

*(E)-5,9-Dibromo-7-styryldibenzo[c,h]acridine (**6m**).* Dark brown liquid. Yield: 323 mg (60%). $R_f$: 0.72 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.70 (d, $J$ = 8.0 Hz, 1H), 8.02−7.98 (m, 3H), 7.84−7.65 (m, 3H), 7.47−7.36 (m, 5H), 7.27−7.15 (m, 2H), 6.94−6.92 (m, 2H), 6.24 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 140.3, 134.7, 133.5, 132.5, 128.7, 128.5, 127.7, 127.2, 127.1, 126.9, 126.2, 126.1, 125.7, 125.6, 122.4, 121.8, 115.5 ppm. HRMS (ESI-TOF) $m/z$: $[M + NH_4]^+$ calcd for $C_{29}H_{21}Br_2N_2$, 555.0066; found, 555.0059.

*(E)-5,9-Dibromo-7-[2-(naphthalen-2-yl)vinyl]dibenzo[c,h]acridine (**6n**).* Dark brown liquid. Yield: 388 mg (66%). $R_f$: 0.56 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.43 (d, $J$ = 8.0 Hz, 2H), 9.04 (d, $J$ = 4.4 Hz, 2H), 8.23−8.19 (m, 2H), 7.95−7.76 (m, 6H), 7.61−7.57 (m, 4H), 7.43−7.27 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 151.0, 148.2, 147.3, 146.1, 140.7, 139.3, 136.4, 133.4, 131.7, 129.9, 128.9, 128.5, 128.1, 128.9, 127.9, 127.7, 127.3, 125.0, 122.8, 122.7, 117.5 ppm. MS (ESI) $m/z$: 588.41 $[M + H]^+$. Anal. Calcd for $C_{33}H_{19}Br_2N$: C, 67.26; H, 3.25; N, 2.38. Found: C, 67.40; H, 3.33; N, 2.29.

*(E)-5,9-Dibromo-7-[2-(thiophen-2-yl)vinyl]dibenzo[c,h]acridine (**6o**).* Brown liquid. Yield: 327 mg (60%). $R_f$: 0.64 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.49 (s, 1H), 8.41 (d, $J$ = 8.4 Hz, 2H), 8.29 (d, $J$ = 8.4 Hz, 2H), 7.97−7.95 (m, 2H), 7.79−7.77 (m, 2H), 7.71−7.51 (m, 4H), 6.93−6.91 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta$ 159.2, 148.7, 137.9, 134.7, 132.2, 130.2, 130.0, 129.9, 129.2, 129.0, 127.9, 127.1, 126.6, 124.5, 120.2, 113.1 ppm. MS (ESI) $m/z$: 542.31 $[M]^+$. Anal. Calcd for $C_{27}H_{15}Br_2NS$: C, 59.47; H, 2.77; N, 2.57. Found: C, 59.68; H, 2.81; N, 2.49.

*(E)-5,9-Dinitro-7-styryldibenzo[c,h]acridine (**6p**).* Yellow solid. Yield: 287 mg (61%). Mp: 212−214 °C. $R_f$: 0.12 (EtOAc/hexane, 1:19 v/v). $^1H$ NMR (400 MHz, $CDCl_3$): 9.04 (d, $J$ = 8.4 Hz, 2H), 8.45 (d, $J$ = 7.2 Hz, 2H), 8.05 (d, $J$ = 8.4 Hz, 2H), 7.88 (d, $J$ = 8.0 Hz, 2H), 7.62−7.43 (m, 6H), 7.29−7.26 (m, 6H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): 162.4, 155.2, 143.7, 132.5, 130.0, 129.5, 129.1, 128.9, 127.0, 126.1, 125.9, 124.9, 123.3, 111.2 ppm. MS (ESI) $m/z$: 504.34 $[M + MeOH + H]^+$. Anal. Calcd for $C_{29}H_{17}N_3O_4$: C, 73.88; H, 3.63; N, 8.91. Found: C, 73.96; H, 3.56; N, 8.80.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02105.

Copies of $^1H$ and $^{13}C$ NMR spectra for all products **6a**−**p** and the ORTEP plot of the crystal structure of **6a** (PDF)

### Accession Codes

CCDC 1988029 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-1223-336033.

## ■ AUTHOR INFORMATION


### Corresponding Author

**Kannupal Srinivasan** − *School of Chemistry, Bharathidasan University, Tiruchirappalli, Tamil Nadu 620 024, India;* orcid.org/0000-0001-5044-4716; Phone: +91-431-2407053; Email: srinivasank@bdu.ac.in; Fax: +91-431-2407043

### Author

**Murugesan Thangamani** − *School of Chemistry, Bharathidasan University, Tiruchirappalli, Tamil Nadu 620 024, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02105


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors thank the Science and Engineering Research Board (SERB), India, for financial support and DST-FIST for instrumentation facilities at the School of Chemistry, Bharathidasan University. M.T. thanks the University Grants Commission (UGC) for a BSR-RFSMS fellowship.

## ■ REFERENCES


(1) (a) Reissig, H.-U.; Zimmer, R. Donor−acceptor-substituted cyclopropane derivatives and their application in organic synthesis. *Chem. Rev.* **2003**, *103*, 1151−1196. (b) Schneider, T. F.; Kaschel, J.; Werz, D. B. A new golden age for donor-acceptor cyclopropanes. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504−5523. (c) Pagenkopf, B. L.; Vemula, N. Cycloadditions of donor−acceptor cyclopropanes and nitriles. *Eur. J. Org. Chem.* **2017**, *2017*, 2561−2567. (d) Budynina, E. M.; Ivanov, K. L.; Sorokin, I. D.; Melnikov, M. Y. Ring opening of donor−acceptor cyclopropanes with *N*-nucleophiles. *Synthesis* **2017**, *49*, 3035−3068. (e) Singh, P.; Varshnaya, R. K.; Dey, R.; Banerjee, P. Donor-acceptor cyclopropanes as an expedient building block towards the construction of nitrogen-containing molecules. *Adv. Synth. Catal.* **2020**, *362*, 1447−1484. (f) Werz, D. B.; Biju, A. T. Uncovering the neglected similarities of arynes and donor−acceptor cyclopropanes. *Angew. Chem., Int. Ed.* **2020**, *59*, 3385−3398.

(2) (a) Wurz, R. P.; Charette, A. B. Doubly activated cyclopropanes as synthetic precursors for the preparation of 4-nitro and 4-cyano-dihydropyrroles and pyrroles. *Org. Lett.* **2005**, *7*, 2313−2316. (b) Lifchits, O.; Charette, A. B. A mild procedure for the Lewis acid catalyzed ring-opening of activated cyclopropanes with amine nucleophiles. *Org. Lett.* **2008**, *10*, 2809−2812. (c) Zhou, Y. Y.; Wang, L. J.; Li, J.; Sun, X. L.; Tang, Y. Side-arm-promoted highly enantioselective ring-opening reactions and kinetic resolution of donor-acceptor cyclopropanes with amines. *J. Am. Chem. Soc.* **2012**, *134*, 9066−9069. (d) Martin, M. C.; Patil, D. V.; France, S. Functionalized 4-carboxy- and 4-keto-2,3-dihydropyrroles via Ni(II)-catalyzed nucleophilic amine ring-opening cyclizations of cyclopropanes. *J. Org. Chem.* **2014**, *79*, 3030−3039. (e) Kim, A.; Kim, S.-G. Lewis-acid-catalysed Friedel−Crafts alkylation of donor−acceptor cyclopropanes with electron-rich benzenes to generate 1,1-diarylalkanes. *Eur. J. Org. Chem.* **2015**, *2015*, 6419. (f) Xia, Y.; Liu, X.; Zheng, H.; Lin, L.; Feng, X. Asymmetric synthesis of 2,3-dihydropyrroles by ring-opening/cyclization of cyclopropyl ketones using primary amines. *Angew. Chem., Int. Ed.* **2015**, *54*, 227−230. (g) Luo, W.; Sun, Z.; Fernando, E. H. N.; Nesterov, V. N.; Cundari, T. R.; Wang, H. Asymmetric ring-opening of donor-acceptor cyclopropanes with primary arylamines catalyzed by a chiral heterobimetallic catalyst. *ACS Catal.* **2019**, *9*, 8285−8293.

(3) (a) Molinski, T. F. Marine pyridoacridine alkaloids: structure, synthesis and biological chemistry. *Chem. Rev.* **1993**, *93*, 1825−1838. (b) Marshall, K. M.; Barrows, L. R. Biological activities of pyridoacridines. *Nat. Prod. Rep.* **2004**, *21*, 731−751. (c) Arai, M. A.; Koryudzu, K.; Ishibashi, M. Inubosins A, B, and C are acridine akaloids isolated from a culture of *Streptomyces* sp. IFM 11440 with ngn2 promoter activity. *J. Nat. Prod.* **2015**, *78*, 311−314. (d) Gensicka-Kowalewska, M.; Cholewinski, G.; Dzierzbicka, K. Recent developments in the synthesis and biological activity of acridine/acridone analogues. *RSC Adv.* **2017**, *7*, 15776−15804.

(4) (a) Denny, W. A. Acridine derivatives as chemotherapeutic agents. *Curr. Med. Chem.* **2002**, *9*, 1655−1665. (b) Prasher, P.; Sharma, M. Medicinal chemistry of acridine and its analogues. *MedChemComm* **2018**, *9*, 1589−1618.
(5) (a) Joshi-Pangu, A.; Levesque, F.; Roth, H. G.; Oliver, S. F.; Campeau, L.-C.; Nicewicz, D.; DiRocco, D. A. Acridinium-based photocatalysts: a sustainable option in photoredox catalysis. *J. Org. Chem.* **2016**, *81*, 7244−7249. (b) Romero, N. A.; Nicewicz, D. A. Organic photoredox catalysis. *Chem. Rev.* **2016**, *116*, 10075−10166.
(6) (a) Molinos-Gomez, A.; Vidal, X.; Maymo, M.; Velasco, D.; Martorell, J.; Lopez-Calahorra, F. Tautomeric enhancement of the hyperpolarizability in new acridine-benzothiazolylamine based NLO chromophores. *Tetrahedron* **2005**, *61*, 9075−9081. (b) Park, M. S.; Lee, J. Y. Indolo acridine-based hole-transport materials for phosphorescent OLEDs with over 20% external quantum efficiency in deep blue and green. *Chem. Mater.* **2011**, *23*, 4338−4343. (c) Qin, P.; Paek, S.; Dar, M. I.; Pellet, N.; Ko, J.; Gratzel, M.; Nazeeruddin, M. K. Perovskite solar cells with 12.8% efficiency by using conjugated quinolizino acridine based hole transporting material. *J. Am. Chem. Soc.* **2014**, *136*, 8516−8519.
(7) (a) Mileykovskaya, E.; Dowhan, W. Visualization of phospholipid domains in *Escherichia coli* by using the cardiolipin-specific fluorescent dye 10-*N*-nonyl acridine orange. *J. Bacteriol.* **2000**, *182*, 1172−1175. (b) Byvaltsev, V. A.; Bardonova, L. A.; Onaka, N. R.; Polkin, R. A.; Ochkal, S. V.; Shepelev, V. V.; Aliyev, M. A.; Potapov, A. A. Acridine orange: a review of novel applications for surgical cancer imaging and therapy. *Front. Oncol.* **2019**, *9*, 925.
(8) For some recent examples, see: (a) Pang, X.; Lou, Z.; Li, M.; Wen, L.; Chen, C. Tandem arylation/Friedel−Crafts reactions of *o*-acylanilines with diaryliodonium salts: a modular synthesis of acridine derivatives. *Eur. J. Org. Chem.* **2015**, *2015*, 3361−3369. (b) Hu, W.; Zheng, Q.; Sun, S.; Cheng, J. Rh(III)-catalyzed bilateral cyclization of aldehydes with nitrosos toward unsymmetrical acridines proceeding with C−H functionalization enabled by a transient directing group. *Chem. Commun.* **2017**, *53*, 6263−6266. (c) Wang, M.; Fan, Q.; Jiang, X. Nitrogen−iodine exchange of diaryliodonium salts: access to acridine and carbazole. *Org. Lett.* **2018**, *20*, 216−219. (d) Kim, S.; Han, S. H.; Mishra, N. K.; Chun, R.; Jung, Y. H.; Kim, H. S.; Park, J. S.; Kim, I. S. Dual role of anthranils as amination and transient directing group sources: synthesis of 2-acyl acridines. *Org. Lett.* **2018**, *20*, 4010−4014. (e) Wu, H.; Zhang, Z.; Ma, N.; Liu, Q.; Liu, T.; Zhang, G. Synthesis of acridines from *o*-aminoaryl ketones and arylboronic acids by copper trifluoroacetate-mediated relay reactions. *J. Org. Chem.* **2018**, *83*, 12880−12886.
(9) Eicher, T.; Hauptmann, S. *The chemistry of heterocycles. Structures, reactions, synthesis and applications*; Wiley-VCH: Weinheim, 2003.
(10) (a) Fadhel, O.; Pretsch, R.; Rothe, C.; Lessmann, R.; Carddinali, F. WO 2013/079217, June 6, 2013. (b) Kim, M.-S.; Kim, S.-W.; Kim, J.-H.; Chu, C.-W.; Kho, S.-I.; Im, J.-H. US 2015/0034915 A1, Feb 5, 2015.
(11) (a) Cymerman-Craig, J.; Loder, J. W. The chemotherapy of tuberculosis. Part V. Some 5-amino-benzacridines and − dibenzacridines. *J. Chem. Soc.* **1955**, 4309−4314. (b) Lehr, R. E.; Kumar, S.; Shirai, N.; Jerina, D. M. Synthesis of enantiomerically pure bay-region 3,4-diol 1,2-epoxide diastereomers and other derivatives of the potent carcinogen dibenz[*c*,*h*]acridine. *J. Org. Chem.* **1985**, *50*, 98−105.
(12) Flader, A.; Ohlendorf, L.; Ehlers, P.; Ammon, E.; Villinger, A.; Langer, P. Brønsted acid mediated synthesis and properties of dibenzoacridine derivatives. *Adv. Synth. Catal.* **2019**, *361*, 2981−2991.
(13) (a) Sathishkannan, G.; Srinivasan, K. Highly diastereoselective synthesis of 1-pyrrolines *via* $SnCl_4$-promoted [3 + 2] cycloaddition between activated donor-acceptor cyclopropanes and nitriles. *Org. Lett.* **2011**, *13*, 6002−6005. (b) Sathishkannan, G.; Srinivasan, K. Lewis acid− mediated transformations of *trans*-2-aroyl-3-aryl-cyclopropane-1,1-dicarboxylates into 2-pyrones and 1-indanones. *Adv. Synth. Catal.* **2014**, *356*, 729−735. (c) Sathishkannan, G.; Srinivasan, K. 3 + 3] Annulation of donor−acceptor cyclopropanes with mercaptoacetaldehyde: application to the synthesis of tetrasubstituted thiophenes. *Chem. Commun.* **2014**, *50*, 4062−4064. (d) Sathishkannan, G.; Tamilarasan, V. J.; Srinivasan, K. Nucleophilic ring-opening reactions of *trans*-2-aroyl-3-aryl-cyclopropane-1,1-dicarboxylates with hydrazines. *Org. Biomol. Chem.* **2017**, *15*, 1400−1406. (e) Thangamani, M.; Srinivasan, K. Lewis acid-mediated ring-opening reactions of *trans*-2-aroyl-3-styrylcyclopropane-1,1-dicarboxylates: access to cyclopentenes and E,E-1,3-dienes. *J. Org. Chem.* **2018**, *83*, 571−577.
(14) Kobayashi, S. Scandium triflate in organic synthesis. *Eur. J. Org. Chem.* **1999**, *1999*, 15−27.
(15) For CCDC 1988029 (compound **6a**), see the Supporting Information for details.
(16) For fragmentation and elimination of the malonate moiety, see: Novikov, R. A.; Tarasova, A. V.; Denisov, D. A.; Borisov, D. D.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. [4 + 2] Annulation of donor−acceptor cyclopropanes with acetylenes using 1,2-zwitterionic reactivity. *J. Org. Chem.* **2017**, *82*, 2724−2738.


https://dx.doi.org/10.1021/acs.joc.0c02105
*J. Org. Chem.* XXXX, XXX, XXX−XXX