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Efficient formation of σ^H-adducts as a key step in the synthesis of acridines via Lewis acid-promoted transformations of the nitro group

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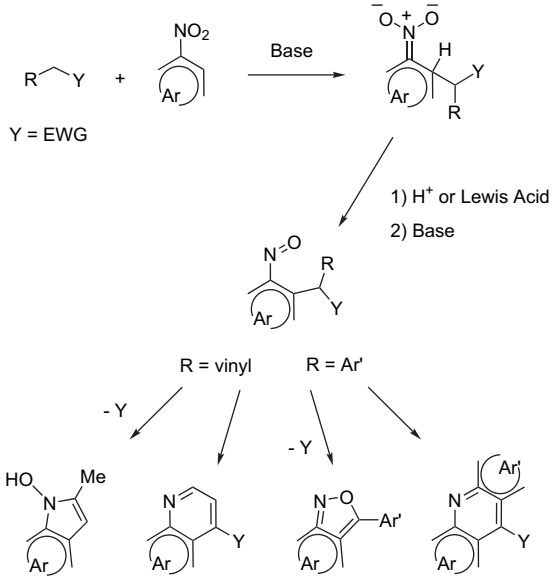
Abstract—A step-by-step methodology was applied in the Lewis acid-promoted synthesis of fused heterocyclic systems from carbanions and nitroarenes. Efficient formation of σ^H-adducts of substituted nitrobenzenes and phenylacetonitrile derivatives followed by reductive transformation of the nitro group with silylating or acylating agents leads to 9-cyanoacridines. The method was found to be superior to the earlier one-pot approach, resulting in better yields and a broader scope of the reaction.

1. Introduction

The synthesis of polycyclic nitrogen heterocycles via one-pot reactions of carbanions or other nucleophiles with nitroaromatic compounds has remained of interest to us for the last decade. The reaction is initialised by the addition of the nucleophile to the nitroarene ring in the *ortho* position to the nitro group, and then leads—depending on the structure of the nucleophilic agent—to substituted quinoline,[1] 1-hydroxyindole[1,2] or 2,1-benzisoxazole[3] systems. When the carbanionic moiety is a part of the nitroarene molecule the intramolecular variant of the reaction furnishes more complex polycyclic heterocyclic structures.[4] In all these processes, the nitrogen atom of the nitro group is incorporated in the new fused heterocyclic ring (Scheme 1). The common intermediates in these reactions seem to be σ^H-adducts of the carbanions to the nitroarenes and corresponding nitroso compounds, which are formed by means of base-induced elimination of water from the σ^H-adducts. The process can be therefore considered as nucleophilic substitution of hydrogen in nitroaromatics.[5] We have found that this conversion is promoted by a combination of the Lewis acids such as $MgCl_2$, R_3SiCl, LiBr, Ti(*i*-OPr)$_4$ and bis(trimethylsilyl)-acetamide and a base (DBU or Et_3N) in aprotic solvents, e.g., MeCN, DMSO and DMF. However, a complex mechanism of the multistep reaction requires careful selection of the basic/acidic reaction components in order to suitably balance both base-promoted and acid-aided reaction steps. It is not surprising, therefore, that there are no general conditions meeting the above requirements for all such reactions and even for different pairs of reagents undergoing a particular reaction. Moreover, only relatively weak basic and acidic reagents can be used together in the reaction mixture, which limit the scope of the reaction.



Scheme 1.

Keywords: Carbanions; Nitroarenes; Heterocycles; Nitroso group; Cyclisation.
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We have recently presented[6] a simple approach to the synthesis of selected fused nitrogen heterocycles from nitroarenes and benzylic-type anion precursors based on Scheme 1. The reaction performed following the one-pot methodology, i.e., mixing both substrates in appropriate solvent with the Lewis acid and DBU as a base, was quite efficient in a few cases, but nevertheless, suffered from the limitations mentioned above. In particular, the base used and the reaction conditions were not appropriate to attain a high concentration of σ^H-adducts. Therefore, the reaction proceeded satisfactorily only between thienylmethyl 4-tolyl sulfone and strongly electrophilic, bicyclic nitroarenes.[6] Several other carbanion precursors, e.g., phenylacetonitrile derivatives, reacted rather poorly.

To overcome the problem, we decided to divide the multistep process into separate steps, which can be performed under more suitable reaction conditions. The crucial point of the process seems to be the efficient formation of σ^H-adducts, which could be then transformed into nitroso compounds under tuned conditions. It is known that under appropriate conditions, σ^H-adducts of nitroarenes and a variety of carbanions—the ultimate intermediates in vicarious[7] and oxidative[8] nucleophilic substitution of hydrogen—can be formed in considerable concentrations, and sometimes even almost quantitatively.[8–11] We have shown lately that σ^H-adducts formed at low temperature from aniline anions and nitroarenes can be transformed into stable nitrosoarenes when treated with proton acids.[12]

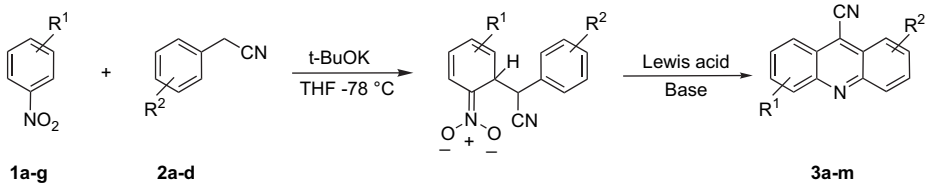
2. Results and discussion

In this paper, we present results of adopting the step-by-step methodology to the formation of fused heterocyclic systems from carbanions and nitroarenes. The reaction between 4-chloronitrobenzene **1a** and phenylacetonitrile **2a**, which gave only 22% yield of 2-chloroacridine-9-carbonitrile when carried out according to the one-pot procedure,[6] was chosen as a model process and a number of procedure variations were tested in order to find the best reaction conditions.

To provide the highest yield of σ^H-adduct, the carbanion of the **2a** was generated at −78 °C in THF with a small excess of *t*-BuOK in the presence of the nitroarene **1a**, the order of added reagents as well as the reaction time being altered in different experiments. The actual extent of σ^H-adduct formation is not possible to estimate directly, and only the yield of stable products resulting from the subsequent transformation can be informative in this respect. Attempted simple transformation of the produced σ^H-adduct into nitroso compound by its protonation, which worked in the described earlier cases of the adducts of aniline anions to nitroarenes[12] and in other cases,[13] failed. The *cine* substitution of the nitro group, observed under the action of acids on some σ^H-adducts,[11] did not proceed either. Thus, complete transformation of the σ^H-adduct to the acridine derivative was performed initially using arbitrary chosen reagents and conditions. They were Me_3SiCl as Lewis acid, and Et_3N as a base, taken in 5-fold excess and added in different order to the σ^H-adduct solution at −78 °C. The mixture was then allowed to warm up and kept at room temperature for 24 h and analysed by HPLC using internal standard to determine the yield of 2-chloroacridine-9-carbonitrile **3a**. The results showed that the σ^H-adduct was formed in less than 4 min. The order of addition of the other reagents did not influence the yield of **3a**, which was 38–42% in all cases. The reaction was by no means complete after the time selected for comparison purpose—after additional 6 days the yield could be increased to 84%. This proves that under the applied conditions the formation of the σ^H-adduct was rather effective. Higher, that is, 20-fold excess of Et_3N resulted in increasing the product yield to 69% after 24 h, which shows that the apparent rate of the subsequent transformations depends on the base concentration. The whole reaction time could be shortened this way, although such a large amount of the base seems to be inconvenient.

The procedure, based on these introductory results, was then used in the reactions of a number of substituted arylacetonitriles and nitrobenzene derivatives leading to substituted acridine-9-carbonitriles (Scheme 2, Table 1, procedure A). The method appears to be an improvement as compared with the previous one, as the yields of several products were substantially increased, and what is even more important, numerous substituted acridines, not available by means of the one-pot methodology, could be synthesised.

Further modifications of the reaction conditions revealed that Me_3SiCl can be replaced with *t*-$BuMe_2SiCl$ with somewhat better results after similar reaction time (Table 1, procedure B), while other silyl chlorides like *t*-$BuPh_2SiCl$, BSA and *t*-$BuMe_2SiOSO_2CF_3$ were much less effective. For procedure B, with *t*-$BuMe_2SiCl$ as a silylating agent, different bases were checked. The observed influence of the Et_3N concentration on the apparent reaction rate was a reason to replace this weak base with the stronger one. As expected, when 5 equiv of DBU was applied instead of Et_3N, the model reaction of **1a** and **2a** was brought to an end after 48 h with 84% yield (HPLC). Even more notable effect was observed when *t*-BuOK was used. In this case, the σ^H-adduct was treated with a 5-fold excess of *t*-$BuMe_2SiCl$, then 1.1 equiv of *t*-BuOK was added and the reaction was complete at room temperature after 48 h. This method was applied to several reactions (Table 1, procedure C) giving



Scheme 2.

Table 1. Substituted acridines **3** from reactions of nitroarenes **1** and arylacetonitriles **2**

Entry	$ArNO_2$		$ArCH_2CN$		Product	Procedure[a]			
						Yield[b]/% (time/days)	Yield[b]/%		
	1	R^1	**2**	R^2	**3**	A	B	C	D
1	**a**	4-Cl	**a**	H	**a**	67 (5)	74	83	77
2	**b**	H	**a**	H	**b**	20 (4)			
3	**c**	4-Br	**a**	H	**c**	67 (1)	74		
4	**d**	4-CF_3	**a**	H	**d**	55 (1)	59	32	17
5	**e**	4-OMe	**a**	H	**e**	12 (6)	9	26	32
6	**f**	2,4-diCl	**a**	H	**f**	19 (3)	8	24	23
7	**g**	3,4-diCl	**a**	H	**g**	61 (6)	49	54	
					h	14 (6)	14	20	
8	**b**	4-Cl	**b**	3,4-diOMe	**i**	66 (2)			
9	**b**	4-Cl	**c**	4-Br	**j**	75 (2)			
10	**h**	4-SPh	**a**	H	**k**		59	32[f]	56
11	**i**	4-F	**a**	H	**l**		50	64	
12	**j**	[g]	**d**	H	**m**	45 (3)			

[a] A: Me_3SiCl/Et_3N; B: *t*-$BuMe_2SiCl/Et_3N$, 6 days; C: *t*-$BuMe_2SiCl$/*t*-BuOK, 48 h; D: *t*-$BuCOCl/Et_3N$, 24 h.
[b] Isolated yield.
[c] Compound **3a** of 2% was obtained in the attempted one-pot reaction.
[d] Compound **3b** of 22% was isolated from the one-pot reaction.[5]
[e] Compound **3c** of 7% was formed in the attempted one-pot reaction.
[f] Corresponding *N*-oxide of 14% was also formed.
[g] 5,5-Dimethyl-1,3-dioxan-2-yl.

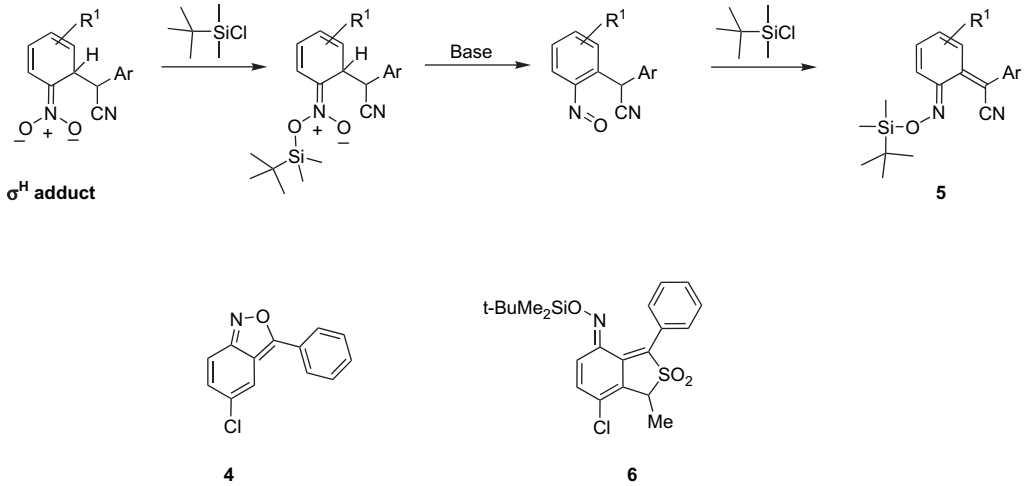
the desired products in comparable yields in a shorter time. The fact that *t*-BuOK succeeded in the presence of an excess of the silylating agent is somewhat surprising. On the other hand, observation that 1 equiv of the base is sufficient to accomplish the reaction is of practical and mechanistic significance. Equally important is a question of the required amount of the silylating agent. When the model reaction of **1a** with **2a** was carried out according to procedure C with the amount of *t*-$BuMe_2SiCl$ altered from 2- to 5-fold excess, the yield of **3a** exceeded 80% after 48 h when at least 3 equiv of the silyl chloride was used. Less amount (2 equiv) of the Lewis acid caused a decrease of the product yield to 30%, which would not change even after prolonged reaction time. Moreover, along with the desired acridine **3a**, a roughly equal amount of benzisoxazole **4** was also produced. Although the formation of the benzisoxazoles as side products in the competitive process was observed earlier, and was influenced by the amount of Lewis acid,[6] the role of silyl chlorides on the reaction pathway needs some deliberation. In contrast to the other (inorganic) Lewis acids used in the reactions shown in Scheme 1, silyl chlorides are believed to form definite covalent bonds with oxygen nucleophiles, thus their stoichiometric amount should be also definite. In the case of the reaction under consideration, silylation of the σ^H-adducts seems to be a plausible first step of the process, followed by the elimination of silanol to form *ortho*-substituted nitrosoarene, similar to elimination of water from the protonated σ^H-adducts formed by aniline anions.[12] This process requires only 1 equiv of the silyl chloride (Scheme 3). The whole reaction apparently needs more equivalents, which suggest that the nitrosoarene so-formed does not cyclise as such. The second equivalent of the silyl chloride could be engaged in the subsequent silylation of the nitroso compound producing its silylated oxime form **5**. Silylated oxime of similar structure (**6**) was unexpectedly obtained earlier in the one-pot, intramolecular reaction of *N*-methyl-*N*-(3-nitroaryl) benzylsulfonamide with DBU and *t*-$BuMe_2SiCl$.[14] Cyclisation of the isolated intermediate to the corresponding acridine required severe conditions, probably due to the strained tricyclic system formation, and was achieved at elevated temperature or under long exposure to light aided with sensitisers and an excess of the silyl chloride.[14]

It can be expected that, in the cases of much less hindered molecules, the cyclisation of the silylated oxime can proceed spontaneously under the reaction conditions at room temperature. It is also reasonable to assume that when the silyl chloride is in deficit, the anion of the nitrosoarene while not silylated undergoes cyclisation to the corresponding benzisoxazole derivative. The role of the third equivalent of the silylating agent remains unclear, however.

Considering the function of silyl chlorides in the course of the reaction, one can suppose that a similar role can be played by acylating agents. Indeed, acylation of the σ^H-adduct with acyl chlorides was found to be even more efficient than silylation and formation of the corresponding acridine-9-carbonitriles was complete after 1–2 h at room temperature. Amongst the acyl chlorides R-COCl tested (R=Me, Ph, COCl, *t*-Bu), pivaloyl chloride was found to be the best. Interestingly, 2-fold excess of the acyl chloride was sufficient to achieve 91% and 81% yields (HPLC) of **3a** in the model reaction carried out analogously to procedures B and C, respectively. In the synthetically aimed reactions (Table 1, procedure D), Et_3N was used as a base and the reactions were carried out for 24 h.

Although the results summarised in Table 1 demonstrate an advantage over the one-pot method, they do not indicate the best procedure among those tested. It seems that the mechanism of the reaction is more complicated and there are some factors in the reaction scheme, which have been not considered so far.

The yields of products **3**, obtained according to the procedure A, are generally similar, regardless of the differences in reactivity of substituted aromatic substrates towards the nucleophiles.[15] Hence, they reflect the expected high equilibrium concentration of the corresponding σ^H-adducts in the first step of the reaction. There are, however, a few exceptions. While a lower yield in the case of **1e** can be rationalised by the strong electronic effect of the 4-methoxy group and thus lower concentration of the corresponding σ^H-adducts, the reason of a reduced efficiency of the reaction of **1f** is less clear. This nitroarene is much more reactive than nitrobenzene and even than **1a** or **1c** in terms of rate



Scheme 3.

constants of the σ^H-adducts' formation,[15] which in turn should assure the higher equilibrium concentration of the adducts. The different results of the reactions of **1f** and also **1e** obtained using various procedures make the problem even more complicated, so this discrepancy calls for further investigation. The lower yield of the reaction of unsubstituted nitrobenzene (**1b**) can be explained by competitive formation of *para* σ^H-adducts, which cannot be transformed into a cyclic product. The reaction of **1i** is worth mentioning as there were no observed products of fluorine substitution, despite the high reactivity of this compound in the S_NAr reactions.[5] Again, fast and efficient formation of σ^H-adducts is responsible for the success of the whole process of the cyanoacridine formation.

Nitroarene **1g** possessing two *ortho* positions available for σ^H-adducts' formation reacted at both sites, with formation of two isomeric acridines with high total yield. Interestingly, the more hindered isomer prevailed. On the other hand, in the reaction of unsymmetrically substituted (3,4-dimethoxyphenyl)acetonitrile (**2b**), when two directions of the cyclisation are possible, only one isomer **3i** was formed.

3. Conclusions

The reductive transformations of the nitro group in σ^H-adducts promoted by the Lewis acids seem to be a very promising approach to the synthesis of various fused heterocyclic systems. The methodology presented in this paper considerably broadens the scope of the reaction by separation of the σ^H-adducts' formation from the subsequent reaction steps. This in turn allows to apply better reaction conditions for different steps of the process and to perform a range of reactions, which so far failed or were not efficient enough. Expanding the step-by-step approach to the subsequent reaction steps, namely elimination reaction and cyclisation of the nitroso intermediate would give an additional possibility to acquire valuable information about the mechanism of the process and is currently in progress.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 Avance (500 MHz) (500 MHz for ^1H and 125 MHz for ^{13}C) and a Varian Mercury 400 (400 MHz for ^1H and 100 MHz for ^{13}C) instruments in $CDCl_3$. Chemical shifts δ are expressed in parts per million referred to TMS and coupling constants in hertz. Mass spectra (EI, 70 eV) were obtained on an AMD-604 spectrometer. IR spectra were recorded on a Perkin–Elmer FTIR Spectrum 2000. HPLC analyses were performed on Shimadzu LC-6A with SPD-6A UV detector at 256 nm, using reverse-phase column LiChrospher© 100 RP-18 (5 μm) and acetonitrile/water eluent. Silica gel Merck 60 (230–400 mesh) was used for flash column chromatography. THF was distilled from sodium/benzophenone ketyl prior to use. 4-(5,5-Dimethyl-1,3-dioxan-2-yl)nitrobenzene (**1j**) was obtained according to the literature.[16] Other reagents were commercially available.

4.2. General procedures for the synthesis of acridine-9-carbonitriles 3a–m

4.2.1. Procedure A. A mixture of nitroarene **1** (2 mmol), arylacetonitrile **2** (2 mmol) and Et_3N (1.0 g, 1.5 mL, 10 mmol) was stirred in dry THF (20 mL) under nitrogen at −78 °C and a solution of *t*-BuOK (270 mg, 2.4 mmol) in THF (5 mL) was added. After 10 min the mixture containing the σ^H-adduct was treated with Me_3SiCl (1.1 g, 1.3 mL, 10 mmol), the cooling bath was removed and the mixture was stirred at room temperature for the time specified in Table 1. The mixture was poured into water (150 mL) and the product, in cases when precipitated, was filtered off, washed with small amount of AcOEt, and then with MeOH and dried. In all cases the aqueous filtrate was extracted with AcOEt (3×50 mL), the extract was combined with the AcOEt filtrate (if applicable), dried over Na_2SO_4 and the solvent was evaporated. From the residue, the product was isolated by column chromatography using toluene/AcOEt 32:1 as eluent, except **3b** and **3f** when hexane/toluene 2:1 system was used.

4.2.2. Procedure B. A solution of nitroarene **1** (2 mmol) and arylacetonitrile **2** (2 mmol) in dry THF (15 mL) was cooled to −78 °C under nitrogen and a solution of *t*-BuOK (246 mg, 2.2 mmol) in THF (5 mL) was slowly added at this temperature. After 10 min of stirring, a solution of *t*-$BuMe_2SiCl$ (1.5 g, 10 mmol) in THF (5 mL) was added, and after the next 20 min, Et_3N (1.0 g, 1.5 mL, 10 mmol) was added. The cooling bath was then removed, the mixture was allowed to warm up to the room temperature and stirred for 6 days. After that, the mixture was poured into saturated aqueous NH_4Cl (150 mL) and worked-up as in procedure A. For isolation of **3k** and **3l**, toluene/AcOEt 16:1 mixture was used as eluent.

4.2.3. Procedure C. The same as procedure B, except that *t*-BuOK (246 mg, 2.2 mmol) in THF (5 mL) was used in place of Et_3N, and that the reaction was carried out at room temperature for 48 h.

4.2.4. Procedure D. The same as procedure B, except that pivaloyl chloride (482 mg, 4 mmol) in THF (5 mL) was used in place of *t*-$BuMe_2SiCl$, and that the reaction was carried out at room temperature for 24 h.

4.2.5. Analytical reactions. In the analytical experiments, carried out according to the above procedure A, B or C, certain amount of diphenyl sulfone as an internal standard was added to the reaction mixture, and the reaction samples taken after specified time were diluted with MeCN and analysed by HPLC. The yields of the products were calculated on the basis of the calibration curves.

4.3. 2-Chloroacridine-9-carbonitrile (3a)

Yield 395 mg, 83% (procedure C). Yellow crystals, mp 208–210 °C (ethanol), lit.[17] mp 208 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.36–8.32 (m, 2H), 8.29 (d, J=8.7 Hz, 1H), 8.24 (d, J=9.3 Hz, 1H), 7.90 (ddd, J=8.7, 6.7, 1.2 Hz, 1H), 7.82–7.77 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 146.6, 135.7, 132.4, 132.1, 131.3, 136.0, 129.8, 126.3, 126.3, 125.1, 123.6, 114.7, 114.3. MS (EI)

m/z 238 (100), 203 (20), 176 (13). IR (KBr): 2225 cm^{-1} (CN). Anal. Calcd for $C_{14}H_7N_2Cl$: C, 70.45; H, 2.96; N, 11.74; Cl, 14.85. Found: C, 70.44; H, 3.00; N, 11.79; Cl, 14.67. HRMS (EI) calculated for $C_{14}H_7N_2{}^{35}Cl$: 238.0298. Found: 238.0302.

4.4. Acridine-9-carbonitrile (3b)

Yield 81 mg, 20% (procedure A). Yellow crystals, mp 186 °C (ethanol), lit.[18] mp 181–182 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.35–8.37 (m, 2H), 8.29–8.32 (m, 2H), 7.88 (ddd, *J*=8.8, 6.6, 1.4 Hz, 2H), 7.77 (ddd, *J*=8.6, 6.6, 1.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 131.0, 130.4, 129.1, 126.1, 125.2, 115.4, 115.0. MS (EI) *m/z* 204 (100), 177 (15). IR (KBr): 2227 cm^{-1} (CN). HRMS (EI) calculated for $C_{14}H_8N_2$: 204.0687. Found: 204.0688.

4.5. 2-Bromoacridine-9-carbonitrile (3c)

Yield 418 mg, 74% (procedure B). Yellow crystals, mp 212–214 °C (ethanol). ^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J*=2.1 Hz, 1H), 8.35 (d, *J*=8.6 Hz, 1H), 8.29 (d, *J*=8.6 Hz, 1H), 8.17 (d, *J*=9.3 Hz, 1H), 7.92 (dd, *J*=9.3, 2.1 Hz, 1H), 7.92 (m, 1H), 7.80 (ddd, *J*=8.6, 6.7, 1.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 146.7, 134.8, 132.0, 131.3, 130.6, 129.8, 127.1, 126.8, 126.3, 125.2, 124.1, 114.7, 114.2. MS (EI) *m/z* 282 (100), 203 (38), 176 (210), 102 (15), 88 (17). IR (KBr): 2223 cm^{-1} (CN). Anal. Calcd for $C_{14}H_7N_2Br$: C, 59.39; H, 2.49; N, 9.89; Br, 28.22. Found: C, 58.78; H, 2.32; N, 9.92; Br, 27.68. HRMS (EI) calculated for $C_{14}H_7N_2{}^{79}Br$: 281.9793. Found: 281.9789.

4.6. 2-Trifluoromethyl-9-carbonitrile (3d)

Yield 320 mg, 59% (procedure B). Yellow crystals, mp 190–191 °C (hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.43 (d, *J*=9.2 Hz, 1H), 8.41 (d, *J*=8.6 Hz, 1H), 8.35 (d, *J*=8.8 Hz, 1H), 8.02 (dd, *J*=9.2, 1.3 Hz, 1H), 7.97 (ddd, *J*=8.8, 6.7, 1.3 Hz, 1H), 7.84 (ddd, *J*=8.6, 6.7, 1.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 148.4, 132.3, 132.0, 130.7 (q, J_{CF}=33.2 Hz), 130.6, 135.5, 126.6, 126.3 (q, J_{CF}=2.7 Hz), 125.4, 124.5, 123.6 (q, J_{CF}=4.8 Hz), 123.5 (q, J_{CF}=273 Hz), 117.2, 114.4. MS (EI) *m/z* 272 (100), 253 (8). IR (KBr): 2224 cm^{-1} (CN). Anal. Calcd for $C_{15}H_7N_2F_3$: C, 66.18; H, 2.59; N, 10.29; F, 20.94. Found: C, 65.98; H, 2.41; N, 10.18; F, 20.76. HRMS (EI) calculated for $C_{15}H_7N_2F_3$: 272.05613. Found: 272.05679.

4.7. 2-Methoxy-9-carbonitrile (3e)

Yield 148 mg, 32% (procedure D). Yellow crystals, mp 177–180 °C (hexane), lit.[19] mp 185 °C (EtOH). ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J*=8.5 Hz, 1H), 8.27 (d, *J*=8.5 Hz, 1H), 8.17 (d, *J*=9.5 Hz, 1H), 7.82 (ddd, *J*=8.5, 6.7, 1.3 Hz, 1H), 7.75 (ddd, *J*=8.5, 6.7, 1.3 Hz, 1H), 7.54 (dd, *J*=9.5, 2.3 Hz, 1H), 7.45 (d, *J*=2.3 Hz, 1H), 4.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 146.4, 145.8, 132.1, 130.4, 129.7, 129.1, 128.2, 126.7, 126.3, 124.7, 115.6, 112.3, 100.3, 56.0. MS (EI) *m/z* 234 (100), 191 (73), 164 (15). IR (KBr): 2222 cm^{-1} (CN). HRMS (EI) calculated for $C_{15}H_{10}N_2O$: 234.0793. Found: 234.0799.

4.8. 2,4-Dichloroacridine-9-carbonitrile (3f)

Yield 130 mg, 24% (procedure C). Yellow crystals, mp 196–198 °C (hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J*=8.8 Hz, 1H), 8.36 (d, *J*=8.8 Hz, 1H), 8.28 (d, *J*=2.1 Hz, 1H), 7.97 (d, *J*=2.1 Hz, 1H), 7.95 (ddd, *J*=8.8, 6.7, 1.2 Hz, 1H), 7.84 (ddd, *J*=8.8, 6.7, 1.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 142.9, 136.1, 134.6, 131.8, 131.7, 131.1, 130.6, 126.9, 126.7, 125.0, 122.8, 115.2, 114.4. MS (EI) *m/z* 272 (100), 237 (13), 202 (26), 175 (10). IR (KBr): 2226 cm^{-1} (CN). HRMS (EI) calculated for $C_{14}H_6N_2{}^{35}Cl_2$: 271.9908. Found: 271.9901.

4.9. 1,2-Dichloroacridine-9-carbonitrile (3g)

Yield 393 mg, 54% (procedure C). Yellow crystals, mp 254–256 °C (ethanol). ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, *J*=8.6, 1.3, 0.7 Hz, 1H), 8.30 (m, 1H), 8.20 (d, *J*=9.3 Hz, 1H), 7.95 (ddd, *J*=8.6, 6.6, 1.3 Hz, 1H), 7.88 (d, *J*=9.3 Hz, 1H), 7.86 (ddd, *J*=8.6, 6.6, 1.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 147.5, 135.1, 131.9, 131.8, 130.8, 130.5, 130.3, 128.2, 127.2, 125.7, 128.3, 115.7, 114.0. MS (EI) *m/z* 272 (100), 237 (15), 202 (26), 175 (10). IR (KBr): 2218 cm^{-1} (CN). Anal. Calcd for $C_{14}H_6N_2Cl_2$: C, 61.57; H, 2.21; N, 10.26; Cl, 25.96. Found: C, 61.67; H, 2.29; N, 10.29; Cl, 25.87. HRMS (EI) calculated for $C_{14}H_6N_2{}^{35}Cl_2$: 271.9908. Found: 271.9915.

4.10. 2,3-Dichloroacridine-9-carbonitrile (3h)

Yield 109 mg, 20% (procedure C). Yellow crystals, mp 246 °C (AcOEt). ^1H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.45 (s, 1H), 8.34 (d, *J*=8.8 Hz, 1H), 8.29 (d, *J*=8.8 Hz, 1H), 7.92 (ddd, *J*=8.8, 6.7, 1.3 Hz, 1H), 7.81 (ddd, *J*=8.8, 6.7, 1.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 146.5, 136.3, 134.6, 131.8, 131.0, 130.6, 130.0, 126.3, 125.5, 125.2, 124.8, 114.5, 114.4. MS (EI) *m/z* 272 (100), 237 (18), 202 (29), 175 (12). IR (KBr): 2226 cm^{-1} (CN). Anal. Calcd for $C_{14}H_6N_2Cl_2$: C, 61.57; H, 2.21; N, 10.26; Cl, 25.96. Found: C, 61.57; H, 2.29; N, 10.01; Cl, 25.74. HRMS (EI) calculated for $C_{14}H_6N_2{}^{35}Cl_2$: 271.9908. Found: 271.9915.

4.11. 7-Chloro-2,3-dimethoxyacridine-9-carbonitrile (3i)

Yield 395 mg, 66% (procedure A). Yellow crystals, mp 262–263 °C (AcOH). ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J*=2.2 Hz, 1H), 8.13 (d, *J*=9.1 Hz, 1H), 7.73 (dd, *J*=9.1, 2.2 Hz, 1H), 7.46 (s, 1H), 7.36 (s, 1H), 4.15 (s, 3H), 4.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 153.7, 146.6, 144.7, 134.1, 131.1, 131.0, 125.1, 124.5, 123.2, 115.2, 110.7, 107.0, 100.8, 16.6, 56.5. MS (EI) *m/z* 300 (33), 298 (100), 283 (11), 255 (30), 192 (24). IR (KBr): 2225 cm^{-1} (CN). HRMS (EI) calculated for $C_{16}H_{11}N_2O_2{}^{35}Cl$: 298.0509. Found: 298.0505.

4.12. 6-Bromo-2-chloroacridine-9-carbonitrile (3j)

Yield 473 mg, 75% (procedure A). Yellow crystals, mp 260 °C (AcOEt). ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (m, 1H), 8.35 (dd, *J*=2.2, 0.5 Hz, 1H), 8.27 (d, *J*=9.4 Hz, 1H), 8.23 (dd, *J*=9.2, 0.5 Hz, 1H), 7.87 (dd, *J*=9.2, 2.0 Hz,

1H), 7.85 (dd, *J*=9.4, 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 147.2, 136.1, 133.4, 133.2, 132.5, 132.1, 126.4, 126.3, 126.1, 124.9, 123.7, 114.8, 114.3. MS (EI) *m/z* 320 (25), 318 (100), 316 (76), 237 (23), 202 (42). IR (KBr): 2227 cm^{-1} (CN). Anal. Calcd for $C_{14}H_6N_2ClBr$: C, 52.95; H, 1.90; N, 8.82. Found: C, 52.95; H, 1.80; N, 8.65. HRMS (EI) calculated for $C_{14}H_6N_2{}^{35}Cl^{79}Br$: 315.9403. Found: 315.9395.

4.13. 2-(Phenylthio)acridine-9-carbonitrile (3k)

Yield 367 mg, 59% (procedure B). Orange crystals, mp 140–142 °C (ethanol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (ddd, *J*=8.7, 1.3, 0.7 Hz, 1H), 8.26 (m, 1H), 8.14 (dd, *J*=9.2, 0.5 Hz, 1H), 8.00 (dd, *J*=2.0, 0.5 Hz, 1H), 7.84 (ddd, *J*=8.7, 6.7, 1.4 Hz, 1H), 7.74 (ddd, *J*=8.7, 6.7, 1.4 Hz, 1H), 7.64–7.59 (m, 3H), 7.50–7.46 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 147.2, 141.2, 134.0, 131.5, 130.7, 130.6, 130.4, 130.0, 129.3, 126.5, 126.4, 125.1, 121.4, 114.9, 113.3. MS (EI) *m/z* 312 (100). IR (KBr): 2216 cm^{-1} (CN). Anal. Calcd for $C_{20}H_{12}SN_2S$: C, 76.90; H, 3.87; N, 8.97; S, 10.26. Found: C, 76.98; H, 3.95; N, 8.95; S, 10.30. HRMS (ES) calculated for $C_{20}H_{12}N_2S$: 312.0721. Found: 312.0726.

4.14. 2-Fluoroacridine-9-carbonitrile (3l)

Yield 283 mg, 64% (procedure C). Yellow crystals, mp 159–160 °C (ethanol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36–8.29 (m, 3H), 7.96 (dd, *J*=8.5, 2.7 Hz, 1H), 7.89 (ddd, *J*=8.5, 6.7, 1.1 Hz, 1H), 7.80 (ddd, *J*=8.5, 6.7, 1.1 Hz, 1H), 7.69 (ddd, *J*=9.6, 8.5, 2.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (d, *J*=254.6 Hz), 147.8 (d, J_{CF}=2.5 Hz), 145.8, 133.6 (d, J_{CF}=9.4 Hz), 130.9 (d, J_{CF}=1.1 Hz), 130.6, 129.8, 126.9 (d, J_{CF}=10.5 Hz), 126.3, 124.9, 122.9 (d, J_{CF}=27.9 Hz), 114.8, 114.6 (d, J_{CF}=8.7 Hz), 107.7 (d, J_{CF}=23.9 Hz). MS (EI) *m/z* 222 (100), 195 (12). IR (KBr): 2227 cm^{-1} (CN). Anal. Calcd for $C_{14}H_7N_2F$: C, 75.67; H, 3.18; N, 12.61; F, 8.55. Found: C, 75.49; H, 3.23; N, 12.47; F, 8.59. HRMS (EI) calculated for $C_{14}H_7N_2F$: 222.0593. Found: 222.0599.

4.15. 2-(5,5-Dimethyl-1,3-dioxan-2-yl)acridine-9-carbonitrile (3m)

Yield 285 mg, 45% (procedure A). Yellow crystals, mp 171–172 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48–8.50 (m, 1H), 8.36–8.39 (m, 1H), 8.33 (d, *J*=9.0 Hz, 1H), 8.30–8.34 (m, 1H), 8.07 (dd, *J*=9.0, 1.8 Hz, 1H), 7.90 (ddd, *J*=8.7, 6.6, 1.4 Hz, 1H), 7.78 (ddd, *J*=8.7, 6.6, 1.1 Hz, 1H), 5.66 (s, 1H), 3.86–3.90 (m, 2H), 3.75–3.79 (m, 2H), 1.35 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 148.5, 139.3, 131.1, 130.6, 130.5, 129.4, 129.1, 126.2, 125.7, 122.8, 115.9, 115.0, 100.7, 77.8, 30.3, 23.1, 21.9. MS (EI) *m/z* 318 (96), 232 (100), 204 (74), 176 (19). Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.40; H, 5.84; N, 8.75.

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