

HETEROCYCLES, Vol. 88, No. 2, 2014, pp. 1433 - 1444. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 12th August, 2013, Accepted, 11th September, 2013, Published online, 17th September, 2013
DOI: 10.3987/COM-13-S(S)110

**FORMATION OF XANTHONE OXIME AND RELATED COMPOUNDS
USING A COMBINATION OF *tert*-BUTYL NITRITE AND POTASSIUM
HEXAMETHYLDISILAZIDE[†]**

**Yusuke Iwama,^a Takahiro Noro,^a Kentaro Okano,^a Hidetsura Cho,^{*a,b} and
Hidetoshi Tokuyama^{*a}**

^aGraduate School of Pharmaceutical Sciences and ^bGraduate School of Science,
Tohoku University, Aramaki, Aoba-ku, Sendai 980-8578, Japan
E-mail: tokuyama@mail.pharm.tohoku.ac.jp, hcho@mail.pharm.tohoku.ac.jp

Abstract – Synthesis of xanthone oxime and related compounds via nitrosation of the dibenzylic position using a combination of *tert*-butyl nitrite and potassium hexamethyldisilazide is described. The reaction conditions are effective for the synthesis of xanthone oxime as well as thioxanthone, acridone, and anthrone oximes, which have been difficult to synthesize from the corresponding ketones by conventional dehydrative condensation with hydroxylamine.

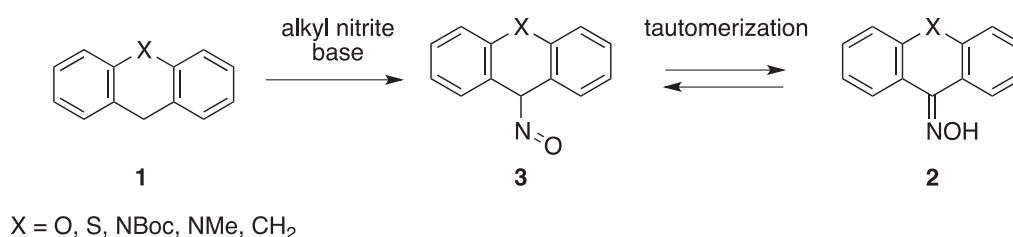
INTRODUCTION

Xanthone, thioxanthone, acridone, and anthrone oximes are highly attractive synthetic precursors for nitrogen-containing heterocycles since Beckmann rearrangement¹ or other ring-expansion reactions² provide the corresponding medicinally attractive nitrogen-containing tricyclic compounds. But despite their potential utility, there is no efficient method for preparation of these oximes. Thus, the conventional dehydrative condensation of the corresponding ketones and hydroxylamine is inefficient due to the low reactivity of the carbonyl group caused by the resonance effects of a heteroatom. Although several examples of dehydrative condensation with hydroxylamine have been documented in the literature, yields of the corresponding oximes were not reported in most cases.³ As an alternative route, a two-step method including conversion of ketone to more reactive thione followed by condensation with hydroxylamine was developed.^{1d,4} In addition to the classical dehydrative condensation of ketones and hydroxylamine, oximes have also been synthesized by several other methods.⁵ For example, nitrosation of alkane under

[†]This paper is dedicated to Professor Dr. Victor Snieckus, Queen's University on the occasion of his 77th birthday.

radical conditions and subsequent tautomerization of the resultant nitroso compound gives the corresponding oxime;^{5c} however, radicalic conditions under photo irradiation⁶ or using a combination of *tert*-butyl nitrite (*t*-BuONO) and *N*-hydroxyphthalimide,⁷ have a limited substrate scope. Nitrosation of enolizable methylene, such as the α -position of carbonyl or cyano groups,⁸ takes place under acidic conditions. Typical conditions such as nitrite salts and strong aqueous acids, however, promote electrophilic nitrosation on an aromatic ring⁹ and are inappropriate for the electron-rich aromatic compounds employed in this study.

With this background, we investigated oximation of **1** to xanthone oxime **2a** and related compounds **2b-2e** via nitroso compound **3** (Scheme 1).^{8a,10} Herein we report a formation of oxime using a combination of *t*-BuONO and potassium hexamethyldisilazide (KHMDS).

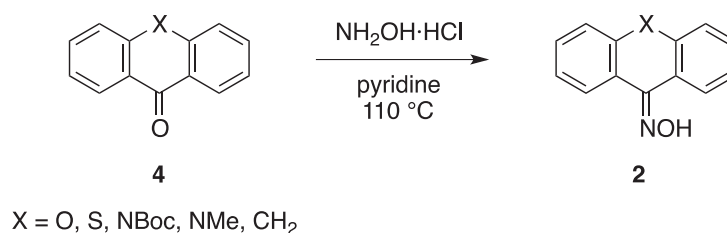


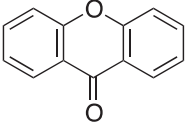
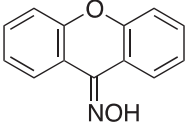
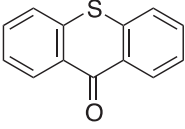
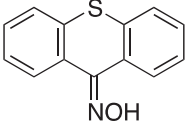
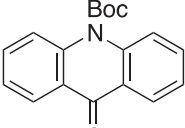
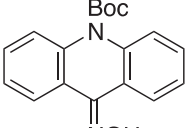
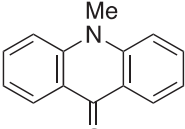
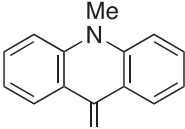
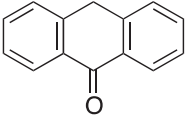
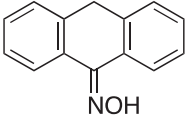
Scheme 1. Formation of Oxime via Tautomerization of Nitroso Compound

RESULTS AND DISCUSSION

At the outset of our research, we carefully investigated the conventional condensation of ketones and hydroxylamine (Table 1). Disappointingly, the reaction rate was slow to provide the corresponding oximes in low to moderate yields with recovery of the starting ketones **4a** and **4b** (entries 1 and 2). *N*-Boc acridone **4c** was completely consumed in 12 h even at 80 °C; however, the desired oxime **2c** was isolated in 21%. Instead, removal of the Boc group took place to provide acridone in 78% yield (entry 3). Reaction using *N*-methylacridone **4d** resulted in recovery of **4d** (entry 4), and on the other hand, reaction of anthrone **4e** provided a complex mixture (entry 5).

Having confirmed the infeasibility of the conventional condensation for preparation of the desired oximes, we investigated our working hypothesis, using xanthene **1a**¹¹ as a substrate (Table 2). First, we examined a variety of bases (2.0 equiv.) using 2.0 equiv. of *t*-BuONO as a nitrosation reagent. While the use of KO*t*-Bu^{10b,10c} provided oxime **2a** in 78% yield with recovery of 6% starting xanthene **1a**, more basic NaH gave none of the desired product **2a** (entries 1 and 2). Alkyl lithium, such as MeLi, *n*-BuLi, and *t*-BuLi, also provided minute amounts of the oxime with recovery of ca. 90% of the starting xanthene **1a** (entries 3–5), which indicated that *t*-BuONO reacted with a base. To circumvent the undesired reaction, we used

Table 1. Formation of Oxime by Condensation of Ketones and Hydroxylamine

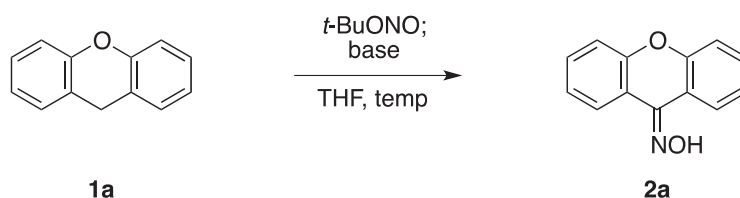
entry	substrates	products	reaction time [h]	yield [%] ^a
1	 4a	 2a	24	44 (56 ^b)
2	 4b	 2b	24	26 (69 ^b)
3 ^c	 4c	 2c	12 ^d	21 (78 ^e)
4	 4d	 2d	24	^f (96 ^b)
5	 4e	 2e	2 ^d	^{f,g}

^a Isolated yield. ^b Recovery of starting ketone. ^c The reaction was carried out at 80 °C. ^d Starting material were completely consumed. ^e Yield of acridone. ^f Not observed. ^g Complex mixture.

hindered bases such as LDA and LiHMDS, and found that hexamethyldisilazide was the better base (entries 6 and 7). During the investigations, we observed a significant effect of counter ion of hexamethyldisilazide. Thus, the use of KHMDS improved the yield of the oxime up to 85% (entries 7–9).

Finally, the desired oxime **2a** was obtained in excellent yield even with the decreased amount (1.2 equiv.) of KHMDS and *t*-BuONO (entry 10).

Table 2. Effects of a Base on Oximation of Xanthene **1a**



entry	Base ([equiv.])	<i>t</i> -BuONO [equiv.]	temp. [°C]	recovery of 1a [%] ^a	yield of 2a [%] ^a
1	KO <i>t</i> -Bu (2.0)	2.0	rt	6	78
2	NaH (2.0)	2.0	rt	88	-
3	MeLi (2.0)	2.0	0	90	-
4	<i>n</i> -BuLi (2.0)	2.0	0	87	4
5	<i>t</i> -BuLi (2.0)	2.0	0	90	4
6	LDA (2.0)	2.0	0	86	2
7	LiHMDS (2.0)	2.0	0	77	8
8	NaHMDS (2.0)	2.0	0	48	32
9	KHMDS (2.0)	2.0	0	-	85
10	KHMDS (1.2)	1.2	0	-	90

^a Isolated yields.

We then focused on feasibility of the established optimal conditions for formation of the variety of oximes (Table 3). In addition to xanthene **1a**, thioxanthene **1b**¹¹ and *N*-Boc-dihydroacridine **1c** were successfully converted to oximes **2b** or **2c** in excellent yields respectively using 1.2 equiv. of *t*-BuONO and KHMDS (entries 2 and 3). In the case of *N*-methyldihydroacridine **1d**,¹² 2.0 equiv. of *t*-BuONO and KHMDS were necessary for complete consumption of **1d** to provide oxime **2d** in 54% yield (entry 4). While dihydroanthracene **1e**¹¹ did not give the desired oxime **2e** under the optimal conditions using KHMDS, the use of *n*-BuLi provided oxime **2e** in moderate yield.

Table 3. Scope and Limitations of Oximation using *t*-BuONO and KHMDS

$\text{X} = \text{O}, \text{S}, \text{NBoc}, \text{NMe}, \text{CH}_2$

entry	substrates	products	yield [%] ^a
1			90 (94 ^b)
2			97
3			93
4			54 ^c
5 ^d			47

^a Isolated yield. ^b *t*-BuONO: 1.5 equiv., KHMDS: 1.5 equiv. ^c *t*-BuONO: 2.0 equiv., KHMDS: 2.0 equiv.

^d To a solution of substrate in THF were added *n*-BuLi (2.0 equiv.) followed by *t*-BuONO (2.0 equiv.) at $-78\text{ }^\circ\text{C}$, and the reaction mixture was stirred for 0.5 h at $-78\text{ }^\circ\text{C}$.

In summary, we have established an efficient synthesis of oximes via nitrosation of dibenzylidene position by using a combination of *t*-BuONO and KHMDS. This method would be an effective choice for oximation of xanthone, thioxanthone, acridone derivatives, and anthrone, which were difficult to be converted to the corresponding oximes by the conventional condensation of ketones with hydroxylamine.

EXPERIMENTAL

General Remarks: Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. All reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Anhydrous THF was purchased from Kanto Chemical Co. Inc. Anhydrous pyridine was dried and distilled according to the standard protocols. Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50 μm) using the indicated eluent. Preparative TLC and analytical TLC were performed on Merck 60 F₂₅₄ glass plates precoated with a 0.25 mm thickness of silica gel. IR spectra were measured on a SHIMADZU FTIR-8300 spectrometer or a JASCO FT/IR-4100 spectrometer. NMR spectra were recorded on a GX500 spectrometer and JNM-AL400 spectrometer. For ¹H NMR spectra, chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ 0) or relative internal CHCl₃ (δ 7.26). For ¹³C NMR spectra, chemical shifts are expressed in ppm downfield from relative internal CDCl₃ (δ 77.0). Mass spectra were recorded on a JEOL JMS-DX-303 spectrometer (EI), a JMS-T100GC spectrometer (EI), or a Bruker micrOTOF II (ESI). Elemental analyses were performed by a Yanaco CHN CORDER MT-5.

***tert*-Butyl 9-oxoacridine-10(9*H*)-carboxylate (4c):** A 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with acridone (402.0 mg, 2.06 mmol) and anhydrous MeCN (6.8 mL). To the solution was added Boc₂O (761.9 mg, 3.49 mmol), followed by DMAP (753.7 mg, 6.17 mmol). The resulting mixture was stirred for 4 h, after which time TLC (hexanes-EtOAc = 4:1) indicated complete consumption of acridone. To the resulting mixture was added H₂O, and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with saturated aqueous NH₄Cl and brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give crude *N*-Boc-acridone **4c**, which was purified by flash silica gel column chromatography (hexanes-EtOAc = 4:1) to afford *N*-Boc-acridone **4c** (565.3 mg, 1.91 mmol, 93%) as a colorless solid. The analytical data (HRMS, ¹H and ¹³C NMR) were identical with those reported in the literature.¹³ R_f = 0.45 (hexanes-EtOAc = 4:1); IR (neat, cm⁻¹): 3446, 1743, 1636, 1604, 1488, 1459, 1369, 1360, 1246, 1178, 1142, 1121, 937, 840, 749, 670, 610, 554.

10-Methylacridin-9(10*H*)-one (4d): A 30-mL flame-dried round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with acridone (398.0 mg, 2.04 mmol) and anhydrous DMF (6.8 mL). To the solution was added NaH (164.0 mg, 4.10 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 30 min. To the resulting mixture was

added MeI (255 μ L, 4.10 mmol) dropwise at 0 °C. The resulting mixture was stirred for 4 h, after which time TLC (hexanes-EtOAc = 1:1) indicated complete consumption of acridone. The reaction mixture was quenched with H₂O, and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with H₂O and brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give crude *N*-methylacridone **4d**, which was purified by flash silica gel column chromatography (hexanes-EtOAc = 4:1) to afford *N*-methylacridone **4d** (410.8 mg, 1.96 mmol, 96%) as a pale yellow solid. The analytical data (IR, HRMS, ¹H and ¹³C NMR) were identical with those reported in the literature.¹⁴ *R*_f = 0.44 (hexanes-EtOAc = 1:1).

Procedure for dehydrative condensation of benzophenones and hydroxylamine.

9*H*-Xanthen-9-one oxime (2a): A 10-mL flame-dried screw-top test tube equipped with a magnetic stirring bar was charged with xanthone **4a** (100.5 mg, 0.512 mmol), NH₂OH·HCl (107.1 mg, 1.54 mmol) and anhydrous pyridine (0.51 mL). The resulting mixture was stirred at 110 °C for 24 h. To the resulting mixture was added H₂O, and the mixture was extracted with EtOAc three times and CH₂Cl₂ once. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give crude xanthone oxime **2a**. Residual pyridine was azeotropically removed with toluene. The residue was purified by flash silica gel column chromatography (CHCl₃) to afford xanthone oxime **2a** (48.0 mg, 0.227 mmol, 44%) as a colorless solid with recovery of xanthone **4a** (56.5 mg, 0.288 mmol, 56%).

9*H*-Thioxanthen-9-one oxime (2b): A 10-mL flame-dried screw-top test tube equipped with a magnetic stirring bar was charged with thioxantone **4b** (101.0 mg, 0.476 mmol), NH₂OH·HCl (99.0 mg, 1.42 mmol) and anhydrous pyridine (0.48 mL). The resulting mixture was stirred at 110 °C for 24 h. To the resulting mixture was added H₂O, and the mixture was extracted with CH₂Cl₂ three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give crude thioxanthone oxime **2b**. Residual pyridine was azeotropically removed with toluene. The residue was purified by flash silica gel column chromatography (CHCl₃ to toluene-Et₂O = 3:2) to afford thioxanthone oxime **2b** (27.9 mg, 0.123 mmol, 26%) as a yellow solid with recovery of thioxanthone **4b** (69.6 mg, 0.328 mmol, 69%).

***tert*-Butyl acridine-10(9*H*)-carboxylate oxime (2c):** A 10-mL flame-dried screw-top test tube equipped with a magnetic stirring bar was charged with *N*-Boc-acridone **4c** (105.6 mg, 0.358 mmol), NH₂OH·HCl (75.1 mg, 1.08 mmol) and anhydrous pyridine (0.36 mL). The resulting mixture was stirred at 80 °C for 12 h after which time TLC (hexanes-EtOAc = 4:1) indicated complete consumption of *N*-Boc-acridone **4c**.

To the resulting mixture was added H₂O, and the mixture was extracted with THF twice and CH₂Cl₂ three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give crude *N*-Boc-acridone oxime **2c**. Residual pyridine was azeotropically removed with toluene. The residue was purified by flash silica gel column chromatography (hexanes-EtOAc = 4:1 to CHCl₃-MeOH = 9:1) to afford *N*-Boc acridone oxime **2c** (23.6 mg, 0.076 mmol, 21%) as a colorless solid with recovery of acridone (54.4 mg, 0.279 mmol, 78%).

A 10-mL flame-dried screw-top test tube equipped with a magnetic stirring bar was charged with *N*-methylacridone (**4d**) (100.7 mg, 0.481 mmol), NH₂OH·HCl (99.6 mg, 1.43 mmol) and anhydrous pyridine (0.48 mL). The resulting mixture was stirred at 110 °C for 24 h. To the resulting mixture was added H₂O, and the mixture was extracted with CH₂Cl₂ three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give crude material. Residual pyridine was azeotropically removed with toluene. Purification by flash silica gel column chromatography (CHCl₃) resulted in only recovery of *N*-methylacridone **4d** (94.6 mg, 0.452 mmol, 94%).

General procedure for constructing oxime via electrophilic nitrosation: A flame-dried 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with starting material (100 mg) and anhydrous THF (0.1 M). To the solution was added 1.2 equiv. of *t*-BuONO at 0 °C, followed by 1.2 equiv. of KHMDS dropwise at 0 °C. The resulting solution was stirred for 30 min, after which time TLC indicated complete consumption of starting material. The reaction was quenched with saturated aqueous NH₄Cl, and the aqueous layer was extracted three times with Et₂O. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material. The residue was purified by flash silica gel column chromatography to afford the desired oxime.

9H-Xanthen-9-one oxime (2a): a colorless solid. *R*_f = 0.48 (hexanes-EtOAc = 4:1); IR (neat, cm⁻¹): 3179, 3033, 2916, 1623, 1594, 1454, 1341, 1257, 998, 932, 738; ¹H NMR (400 MHz, CDCl₃): δ 9.01 (dd, 1H, *J* = 8.4, 1.2 Hz), 8.44 (brs, 1H), 8.00 (dd, 1H, *J* = 8.4, 1.2 Hz), 7.49 (ddd, 1H, *J* = 8.4, 7.2, 1.2 Hz), 7.42 (ddd, 1H, *J* = 8.4, 7.2, 1.2 Hz), 7.36-7.14 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 152.8, 151.5, 141.4, 131.9, 131.6, 130.7, 124.0, 123.8, 122.8, 119.1, 117.3, 117.0, 116.1; HRMS (ESI) Calcd. for C₁₃H₁₀NO₂ (M+H⁺), 212.0706; Found: 212.0711; Anal. Calcd for C₁₃H₉NO₂: C, 73.92; H, 4.29; N, 6.63; Found: C, 73.99; H, 4.39; N, 6.59.

9H-Thioxanthen-9-one oxime (2b): a colorless solid. $R_f = 0.47$ (hexanes-EtOAc = 4:1); IR (neat, cm^{-1}): 3174, 3042, 2906, 1587, 1435, 992, 923, 755, 727; ^1H NMR (400 MHz, CDCl_3): δ 8.57 (brs, 1H), 8.41 (dd, 1H, $J = 8.0, 2.4$ Hz), 7.84 (dd, 1H, $J = 8.0, 1.6$ Hz), 7.51 (dd, 1H, $J = 7.6, 2.4$ Hz), 7.43 (dd, 1H, $J = 7.6, 1.6$ Hz), 7.40–7.28 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.0, 134.1, 132.6, 131.4, 131.0, 129.4, 128.8, 126.7, 126.5, 125.8, 125.6, 125.4 (one carbon is missing due to overlap); HRMS (ESI) Calcd. for $\text{C}_{13}\text{H}_{10}\text{NOS}$ ($\text{M}+\text{H}^+$), 228.0478; Found: 228.0483; Anal. Calcd for $\text{C}_{13}\text{H}_9\text{NOS}$: C, 68.70; H, 3.99; N, 6.16; Found: C, 68.87; H, 4.10; N, 6.15.

tert-Butyl acridine-10(9H)-carboxylate (1c): A two-necked 20-mL round-bottomed flask equipped with a magnetic stirring bar was charged with acridone (195 mg, 1.00 mmol), and THF (2.5 mL). To the solution was added $\text{BH}_3 \cdot \text{THF}$ (1.08 M in THF, 1.3 mL, 1.4 mmol) at room temperature. The reaction mixture was heated to reflux for 4 h, after which time TLC (hexanes-EtOAc = 3:1) indicated complete consumption of acridone. The reaction was quenched with brine and 2 M aqueous NaOH, and the mixture was extracted with Et_2O three times. The combined organic extracts were washed with saturated aqueous NaHCO_3 , dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford the crude dihydroacridine as a colorless solid, which was used for the next reaction without further purification.

A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with dihydroacridine, Boc_2O (766 mg, 3.51 mmol), and MeCN (3.3 mL). To the solution was added DMAP (203 mg, 1.66 mmol) at 0 °C. The solution was stirred for 11 h at room temperature, after which time TLC (hexanes-EtOAc = 9:1) indicated complete consumption of dihydroacridine. The reaction was diluted with Et_2O . The mixture was washed with saturated aqueous NH_4Cl and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes-EtOAc = 9:1) to afford *N*-Boc-dihydroacridine **1c** (226 mg, 0.803 mmol, 80%) as colorless crystals; $R_f = 0.47$ (hexanes-EtOAc = 9:1); IR (neat, cm^{-1}): 1706, 1476, 1328, 1269, 1253, 1151, 760; ^1H NMR (400 MHz, CDCl_3): δ 7.63 (d, 2H, $J = 8.0$ Hz), 7.36–7.17 (m, 4H), 7.12 (d, 2H, $J = 7.2$ Hz), 3.80 (s, 2H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3): δ 152.5, 138.8, 133.0, 126.9, 125.9, 125.04, 124.96, 33.8, 28.2, 27.9; HRMS (ESI): Calcd. for $\text{C}_{14}\text{H}_{12}\text{NO}_2$ [$(\text{M}-t\text{-Bu})^+$], 226.0863; Found: 226.0878; Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_2$: C, 76.84; H, 6.81; N, 4.98; Found: C, 76.64; H, 6.83; N, 5.01.

tert-Butyl 9-(hydroxyimino)acridine-10(9H)-carboxylate oxime (2c): a colorless solid. $R_f = 0.35$ (hexanes-EtOAc = 4:1); IR (neat, cm^{-1}): 3071, 2974, 2928, 1716, 1598, 1463, 1322, 1251, 1159, 955, 923,

755; ^1H NMR (400 MHz, CDCl_3): δ 8.42 (dd, 1H, $J = 8.0, 1.2$ Hz), 8.23 (brs, 1H), 7.79 (d, 1H, $J = 8.0$ Hz), 7.78 (d, 1H, $J = 8.0$ Hz), 7.72 (dd, 1H, $J = 8.0, 1.2$ Hz), 7.41 (ddd, 1H, $J = 8.0, 8.0, 1.2$ Hz), 7.39 (ddd, 1H, $J = 8.0, 8.0, 1.2$ Hz), 7.27 (dd, 1H, $J = 8.0, 8.0$ Hz), 7.24 (dd, 1H, $J = 8.0, 8.0$ Hz), 1.53 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 152.0, 146.4, 138.5, 137.5, 129.2, 129.0, 128.3, 128.2, 125.47, 125.42, 124.7, 124.6, 124.3, 124.2, 82.9, 28.1; HRMS (ESI) Calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$), 311.1390; Found: 311.1386; Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$: C, 69.66; H, 5.85; N, 9.03; Found: C, 69.79; H, 5.81; N, 8.94.

10-Methylacridin-9(10H)-one oxime (2d): a yellow solid. $R_f = 0.28$ (hexanes-EtOAc = 4:1); IR (neat, cm^{-1}): 3004, 2891, 1593, 1464, 1362, 1265, 1175, 989, 918, 744; ^1H NMR (400 MHz, CDCl_3): δ 8.81 (d, 1H $J = 8.4$ Hz), 7.95 (dd, 1H, $J = 8.4, 1.6$ Hz), 7.46 (ddd, 1H, $J = 8.4, 7.2, 1.6$ Hz), 7.43 (ddd, 1H, $J = 8.4, 7.2, 1.6$ Hz), 7.22–7.05 (m, 4H), 3.57 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 145.5, 142.3, 140.7, 131.2, 130.8, 129.8, 124.7, 121.3, 120.6, 119.6, 116.8, 113.4, 113.1, 34.0; HRMS (ESI) Calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}$ ($\text{M}+\text{H}^+$), 225.1022; Found: 225.1018; Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$: C, 74.98; H, 5.39; N, 12.49; Found: C, 74.89; H, 5.45; N, 12.27.

Anthracen-9(10H)-one oxime (2e): A two-necked 30-mL round-bottomed flask equipped with a magnetic stirring bar was charged with dihydroanthracene **1e** (100.2 mg, 0.556 mmol) and anhydrous THF (5.6 mL). To the solution was added *n*-BuLi (1.51 M in *n*-hexane, 0.736 mL, 1.11 mmol) dropwise at -78 °C. The resulting suspension was stirred for 5 min. To the mixture was added *t*-BuONO (0.132 mL, 1.11 mmol) at -78 °C. After the resulting solution was stirred for 30 min, the reaction was quenched with saturated aqueous NH_4Cl , and the aqueous layer was extracted three times with Et_2O . The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexanes-acetone = 6:1) to afford oxime **2e** (54.5 mg, 0.260 mmol, 47%) as a colorless solid. $R_f = 0.43$ (hexanes-EtOAc = 4:1); IR (neat, cm^{-1}): 3063, 2917, 1450, 1331, 1160, 995, 928, 722, 711; ^1H NMR (400 MHz, CDCl_3): δ 8.53 (dd, 1H, $J = 6.8, 2.0$ Hz), 8.12 (brs, 1H), 7.86 (d, 1H, $J = 6.8$ Hz), 7.44–7.28 (m, 6H), 4.01 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.4, 138.1, 135.9, 132.9, 130.6, 129.6, 128.7, 127.9, 127.9, 127.4, 126.9, 126.0, 124.8, 35.5; HRMS (ESI) Calcd. for $\text{C}_{14}\text{H}_{12}\text{NO}$ ($\text{M}+\text{H}^+$), 210.0913; Found: 209.0910; Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{NO}$: C, 80.36; H, 5.30; N, 6.69; Found: C, 80.13; H, 5.36; N, 6.60.

ACKNOWLEDGMENTS

This work was financially supported by the Ministry of Education, Culture, Sports, Science, and Technology, Japan; the KAKENHI, a Grant-in-Aid for Scientific Research (B) (20390003) and (C)

(23590001); the Cabinet Office, Government of Japan through its “Funding Program for Next Generation World-Leading Researchers (LS008)”; JSPS predoctoral fellowship for Y.I.; Tohoku University Global COE program ‘International Center of Research and Education for Molecular Complex Chemistry’.

REFERENCES AND NOTES

- (a) L. G. Donaruma and W. Z. Heldt, *Org. React.*, 1960, **11**, 1; (b) R. E. Gawley, *Org. React.*, 1988, **35**, 1; (c) R. H. Williams and H. R. Snyder, *J. Org. Chem.*, 1973, **38**, 809; (d) K. Nagarajan, C. L. Kulkarni, and A. Venkateswarlu, *Ind. J. Chem.*, 1974, **12**, 247; (e) A. K. Sinha and S. Nizamuddin, *Ind. J. Chem. Sect. B*, 1984, **23**, 165.
- (a) Y. Girault, M. Decouzon, and M. Azzaro, *Bull. Soc. Chim. Fr.*, 1975, 385; (b) K. Hattori, Y. Matsumura, T. Miyazaki, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, 1981, **103**, 7368; (c) S. Sasatani, T. Miyazaki, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, 1983, **24**, 4711; (d) J. Fujiwara, H. Sano, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, 1984, **25**, 2367; (e) K. Maruoka and H. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 668; (f) Y. Torisawa, T. Nishi, and J. Minamikawa, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 387; (g) N. Willand, T. Beghyn, G. Nowogrocki, J.-C. Gesquiere, and B. Deprez, *Tetrahedron Lett.*, 2004, **45**, 1051; (h) M. Ortiz-Marciales, L. D. Rivera, M. De Jesús, S. Espinosa, J. A. Benjamin, O. E. Casanova, I. G. Figueroa, S. Rodríguez, and W. Correa, *J. Org. Chem.*, 2005, **70**, 10132; (i) P. P. Mukhopadhyay, O. Miyata, and T. Naito, *Synlett*, 2007, 1403; (j) O. Miyata, T. Ishikawa, M. Ueda, and T. Naito, *Synlett*, 2006, 2219; (k) H. Cho, K. Murakami, H. Nakanishi, H. Isoshima, K. Hayakawa, and I. Uchida, *Heterocycles*, 1998, **48**, 919; (l) H. Cho, K. Murakami, H. Nakanishi, A. Fujisawa, H. Isoshima, M. Niwa, K. Hayakawa, Y. Hase, I. Uchida, H. Watanabe, K. Wakitani, and K. Aisaka, *J. Med. Chem.*, 2004, **47**, 101; (m) H. Cho, Y. Iwama, K. Sugimoto, E. Kwon, and H. Tokuyama, *Heterocycles*, 2009, **78**, 1183; (n) H. Cho, Y. Iwama, K. Sugimoto, S. Mori, and H. Tokuyama, *J. Org. Chem.*, 2010, **75**, 627; (o) H. Cho, Y. Iwama, N. Mitsuhashi, K. Sugimoto, K. Okano, and H. Tokuyama, *Molecules*, 2012, **17**, 7348; (p) H. Cho, Y. Iwama, K. Okano, and H. Tokuyama, *Synlett*, 2013, 813.
- (a) T. Kurihara and H. Niwa, *Yakugaku Zasshi* 1953, **73**, 1378 [*Chem. Abstr.*, 1955, 313]; (b) N. Campbell, S. R. McCallum, and D. J. Mackenzie, *J. Chem. Soc.*, 1957, 1922; (c) J. Lalevee, X. Allonas, F. Louerat, J.-P. Fouassier, H. Tachi, A. Izumitani, M. Shirai, and M. Tsunooka, *Phys. Chem. Chem. Phys.*, 2001, **3**, 2721; (d) Y. S. Or, Y. Sun, and Z. Wang, WO2007 146695 A1; (e) Y. Sun, D. Niu, G. Xu, Y. S. Or, and Z. Wang, US2007 0281884 A1; (f) Y. Sun, Y. S. Or, and Z. Wang, US2008 187516 A1.
- (a) F. G. Mann and J. H. Turnbull, *J. Chem. Soc.*, 1951, 757; (b) V. A. Prabhu, R. G. Brown, and J. N. Delgado, *J. Pharm. Sci.*, 1981, **70**, 558.

5. (a) R. H. Williams and H. R. Snyder, *J. Org. Chem.*, 1971, **36**, 2327; (b) M. Hafiz and G. A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1700; (c) R. SanMartín, R. Olivera, E. M. de Marigorta, and E. Domínguez, *Tetrahedron*, 1995, **51**, 5361; (d) M. Yonekawa, Y. Koyama, S. Kuwata, and T. Takata, *Org. Lett.* 2012, **14**, 1164.
6. (a) E. V. Lynn, *J. Am. Chem. Soc.*, 1919, **41**, 368; (b) E. V. Lynn and O. Hilton, *J. Am. Chem. Soc.*, 1922, **44**, 645; (c) E. V. Lynn and H. L. Arkley, *J. Am. Chem. Soc.*, 1923, **45**, 1045.
7. (a) T. Hirabayashi, S. Sakaguchi, and Y. Ishii, *Angew. Chem. Int. Ed.*, 2004, **43**, 1120; (b) Y. Ishii, S. Sakaguchi, and T. Iwahama, *Adv. Synth. Catal.*, 2001, **343**, 393.
8. (a) O. Touster, *Org. React.*, 1953, **7**, 327; (b) J. Beger and C. Thielemann, *J. Prakt. Chem.*, 1981, **323**, 137; (c) J. Beger and C. Thielemann, *J. Prakt. Chem.*, 1981, **323**, 337; (d) R. N. Loeppky, J. Shi, C. L. Barnes, and S. Geddam, *Chem. Res. Toxicol.*, 2008, **21**, 295.
9. (a) E. Bosch and J. K. Kochi, *J. Org. Chem.*, 1994, **59**, 5573; (b) R. J. Maleski, M. Kluge, and D. Sicker, *Synth. Commun.*, 1995, **25**, 2327; (c) M. González-Jiménez, J. Arenas-Valgañón, E. Calle, and J. Casado, *Org. Biomol. Chem.*, 2011, **9**, 7680.
10. (a) A. D. Dunn and K. I. Kinnear, *J. Heterocycl. Chem.*, 1985, **22**, 311; (b) M. Le Rudulier and C. Moinet, *J. Organomet. Chem.*, 1988, **352**, 337; (c) M. C. Senechal-Tocquer, D. Senechal, J. Y. Le Bihan, D. Gentric, B. Caro, M. Gruselle, and G. Jaouen, *J. Organomet. Chem.*, 1992, **433**, 261.
11. Xanthene **1a**, thioxanthene **1b**, and dihydroanthracene **1e** are commercially available compounds.
12. *N*-Methyldihydroacridine **1d** was prepared from known procedure, which is described in following paper; Á. Pintér, A. Sud, D. Sureshkumar, and M. Klussmann, *Angew. Chem. Int. Ed.*, 2010, **49**, 5004.
13. A. A. Kulago, E. M. Mes, M. Klok, A. Meetsma, A. M. Brouwer, and B. L. Feringa, *J. Org. Chem.*, 2010, **75**, 666.
14. X.-A. Li, H.-L. Wang, and S.-D. Yang, *Org. Lett.*, 2013, **15**, 1794.