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A new method of bromination of aromatic rings by an *iso*-amyl nitrite/HBr system

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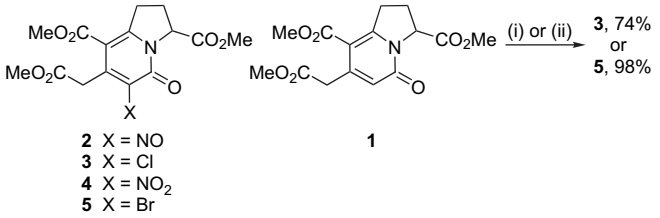
ABSTRACT

A mixture of *iso*-amyl nitrite/HBr is shown to be a mild and efficient reagent for electrophilic aromatic bromination. The reaction succeeds with slightly activated arenes and heterocyclic compounds. By using HCl instead of HBr, chlorination can also be performed in few cases. The *i*-amONO$_2$/HBr mixture can also be utilized for bromination in the α-position of electron withdrawing groups. A possible mechanism is briefly discussed.

1. Introduction

Recently, a mishmash between some experimental results from our students led us to describe that a mixture of indolizine **1**, 37% HCl and *iso*-amyl nitrite yielded nitroso product **2**.[1] Actually, when we tried to repeat this reaction, we observed that the isolated solid was not the nitroso pyridone **2**, but chlorinated triester **3**, and that the compound subjected to elemental analysis was the impure nitro analogs **4** (a product synthesized by another reaction sequence[1]). By a similar procedure using 48% HBr instead of 37% HCl, bromopyridone **5** was obtained in a very good yield of 98% (Scheme 1).



2 X = NO
3 X = Cl
4 X = NO_2
5 X = Br

1

Scheme 1. Reaction conditions: (i) *iso*-amyl nitrite (3.4 equiv), 37% HCl (1.2 equiv), THF, 20 °C, 15 h; (ii) *iso*-amyl nitrite (2 equiv), 48% HBr (1.5 equiv), CH_2Cl_2, 20 °C, 3 h.

To the best of our knowledge, no aromatic halogenation method using a hydrohalide acid as a reagent and an organic nitrite as a co-reagent had been depicted: only a 'bromination impurity at the 5-position of the thiophene ring' was reported during the oxidation of 2-thiophene carbinol into its corresponding ketone by a mixture of *tert*-butyl nitrite, HBr, oxygen and TEMPO[2] (oxidation of a variety of alcohols to ketones is possible with these reagents;[2] in addition, *iso*-amyl nitrite has already been reported to give nitroso aromatic products[3]).

Halogenated compounds can be found in many pharmaceutical products[4] or are used as key intermediates for organic reactions such as metal-catalyzed carbon–carbon bond formations[5] and nucleophilic substitution reactions.[6] Aryl bromides are usually synthesized by electrophilic substitution of arenes with molecular bromine,[7] sometimes with transition metal catalysts. These reactions involve several environmental drawbacks because of the toxic nature of the reagents and the formation of HBr as a by-product.[7–9] Moreover, when using bromine, only half of the Br atoms are utilized and the others turn into hydrohalic acid, reducing the atom efficiency by 50%. Brominating agents such as quaternary ammonium salts of trihalides[10] or NBS[11] in the presence of Brönsted[12] or Lewis acid[13] have been developed to facilitate handling, but their synthesis still requires bromine.

New methods of bromination have been developed to overcome these problems, involving in situ preparation of Br^+ by oxidation of the halogen anion. These approaches are bromine atom economic, and can be realized by using non-pollutant oxidizing agents. The bromine sources are generally an inorganic bromide,[14–18]

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$R_4N^+Br^-$[16,19,20] or HBr,[16,21–25] and the oxidant can be H_2O_2,[19,21–25] TBHP,[22] $NaNO_2/O_2$,[26] Oxone,[27] $NaBO_3$,[14] $Fe(NO_3)_3\cdot1.5N_2O_4/C$,[15] CAN,[28] $(R_4N^+)_2\cdot S_2O_8^{2-}$,[18] $PhI(OAc)_2$,[17] IBX amide resin,[20] methyltrioxorhenium,[29] or HNO_3,[16] sometimes in the presence of catalyst such as V_2O_5,[19] $R_4N^+Br^-$,[20,21] or ammonium molybdate.[14] The use of *t*-BuOCl or *t*-BuOBr in the presence of zeolites has also been described.[30–32]

Since *iso*-amyl nitrite is a readily accessible, stable and non-polluting agent, and because of the novelty of its use in conjunction with a hydrohalic acid to achieve halogenation, we decided to investigate the potential of this reagent as an oxidant in oxyhalogenation reactions.

2. Results and discussion

2.1. Influence of the solvent

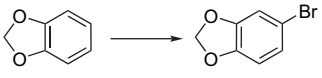
Investigation on the influence of the solvent was realized by reacting 1,3-benzodioxole **6** with 2 equiv of *iso*-amyl nitrite and 1.5 equiv of 48% HBr, at room temperature for 3 h (Table 1). All the solvents lead to pure 4-bromobenzodioxole **7** without detectable impurities; as shown in Table 1, dichloromethane leading to 90% of **7** proves to be the best solvent and was thus selected to perform oxybrominations described in the next part of this paper.[33]

2.2. Oxybromination of various substrates

The arenes that we have chosen for the oxybrominations was listed in Table 2. They are representative of activated and inactivated aromatics, as well as compounds of moderate activity or taken from our laboratory library. All reactions were realized at room temperature, by using 2 equiv of *iso*-amyl nitrite and 1.5 equiv of 48% HBr. In these conditions, no regioselectivity was observed for electron rich *N*,*N*-dimethylaniline or phenols, which led to mixture of mono and poly-brominated products (entries 4, 5 and 7). 1,2-Methylenedioxybenzene gave a quantitative amount of 4-bromobenzodioxole **7** (entry 1) (71% from LiBr/$PhI(OAc)_2$/THF[17]), and reaction of less activated naphthalene yielded 85% of 1-bromonaphthalene in 8 h (entry 3). This needs to be compared with the result of other literature reactions: no reaction from $Et_4N^+Br^-$/IBX amide resin/CH_2Cl_2,[20] 60% yield from the mixture HBr/H_2O_2/CH_2Cl_2/H_2O[23] or 52% from HBr/HNO_3/TBAC/dichloroethane,[16] while with NaBr/$Fe(NO_3)_3\cdot1.5N_2O_4$/C/CH_2Cl_2 20% of 1-nitronaphthalene goes with 70% of the bromo product.[15] The reaction concerning toluene is very instructive; indeed it led to 84% of an 80/20 mixture of *para*/*ortho* bromotoluene. These yields and selectivity are superior to those described in literature for rather similar reactions: no bromination occurred with LiBr or $Et_4N^+Br^-$ and hypervalent iodine compounds[17,20] or $(R_4N^+)_2\cdot S_2O_8^{2-}$,[18] while yields were only 40% (*para*/*ortho*: 66/34) with HBr/HNO_3/TBAC/dichloroethane,[16] and selectivity was only 60/40 with $PyH^+BrCl_2^-$/MeOH[10b] or NaBr/$Fe(NO_3)_3\cdot1.5N_2O_4$/C/CH_2Cl_2.[15]

On the other hand, less reactive arenes such as chlorobenzene or 4-methoxyacetanilide did not react in these conditions (entries 8 and 9). As for the lack of reactivity of quinoline (entry 6), it probably indicates the formation of inert hydrobromide ammonium salt. Acid sensitive 2-methylfuran was entirely decomposed, leading to a mixture of unidentified products (entry 10).

Table 1
Oxybromination of benzodioxole in different solvents

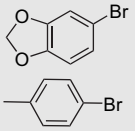
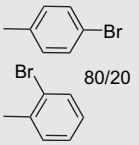
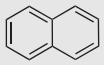
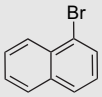
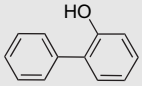
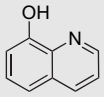
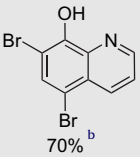
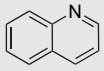
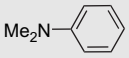
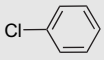
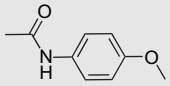
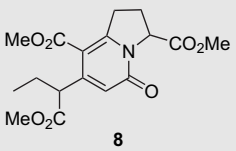
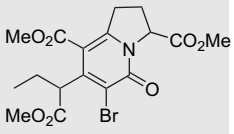
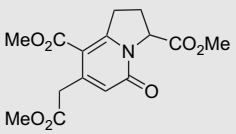
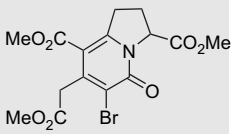
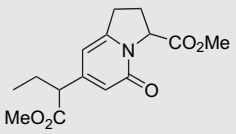
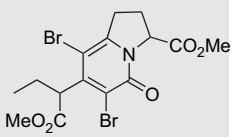


6 **7**

Entry	Solvents[a]	Conversion[b] (%)
1	CH_2Cl_2	90
2	MeCN	77
3	EtOH	69
4	THF	62

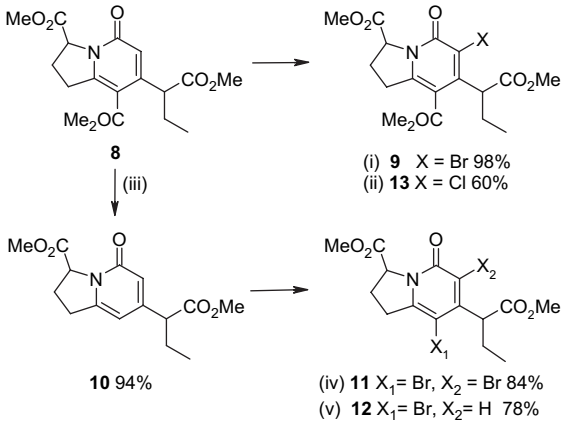
[a] Reaction conditions: *iso*-amyl nitrite (2 equiv), HBr (1.5 equiv), 1 mmol/mL of solvent, 3 h, rt.
[b] ^1H NMR yields.

Table 2
Oxybromination of selected substrates

Entry	Substrates	Yield[a] (%)	Time (h)	Products
1		100	4	
2		84	48	 80/20
3		85	8	
4		100	16	Mixture of many unidentified products
5		100	16	 70%[b]
6		NR	72	
7		100		Mixture of many unidentified products
8		NR	72	
9		NR	48	
10		100	16	Decomposition
11	 **8**	98	5	 **9**
12	 **1**	98	3	 **5**
13	 **10**	84	5	 **11**

[a] ^1H NMR yields.
[b] Accompanied by 15% of *ortho* and 15% of *para* monobromo compounds.

Perhaps the more interesting result was the easiness of formation and very good yields obtained starting from the functionalized indolizinones described in entries 11–13. Indeed, bromopyridone **5** was obtained in the same 96% yield as from $Br_2/KHCO_3/CH_2Cl_2/H_2O$ method (Scheme 1),[1a] and its ethyl analogue **8**[1a] led only to 80% of less pure product **9** when subjected directly to Br_2 versus 98% by using our HBr/*iso*-amyl nitrite system (Scheme 2) (see Section 4). Moreover, the bromination of indolizinone **10** led to 84% yield of dibromo compound **11** with 2 equiv of HBr. Using 1 equiv of HBr, the same reaction leads to 78% of *para* bromo compound **12** accompanied with 13% of an unidentified unbrominated product (Scheme 2).



Scheme 2. Reaction conditions: (i) *iso*-amyl nitrite (2 equiv), 48% HBr (1.5 equiv), CH_2Cl_2, 20 °C, 5 h; (ii) *iso*-amyl nitrite (3 equiv), 37% HCl (1.5 equiv), THF, 20 °C, 7 days; (iii) (a) 48% HBr, reflux, 5 h; (b) MeOH, $MeSO_3H$, $CHCl_3$, molecular sieves 3 Å, reflux, 48 h; (iv) *iso*-amyl nitrite (2 equiv), 48% HBr (2 equiv), CH_2Cl_2, 20 °C, 5 h; (v) *iso*-amyl nitrite (2 equiv), 48% HBr (1 equiv), CH_2Cl_2, 20 °C, 4 h.

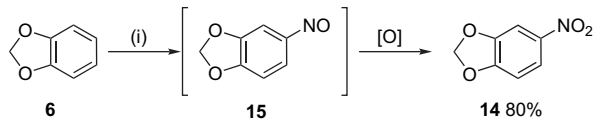
2.3. Other attempted halogenation of arenes with the *iso*-amyl nitrite/HX system

Direct and regioselective halogenation of arenes has recently been described by using the $NaI/Fe(NO_3)_3\cdot 1.5\ N_2O_4/C/CH_2Cl_2$ system.[15] This led us to try iodination of the majority of compounds of Table 2 by the method of HI/*iso*-amyl nitrite/CH_2Cl_2. However, no reaction was observed even with 3 equiv of reagent. In the same way, oxidation of HCl with H_2O_2 has been reported for oxychlorination of activated aromatics[22,23] but 3 equiv of HCl/*iso*-amyl nitrite in CH_2Cl_2 at room temperature did not allow halogenation of compounds of Table 2. Even the very reactive 1,2-dimethoxybenzene did not react; only chlorination of indolizines **1** and **8** was successful, but 1 week was necessary to obtain 60% of chloropyridone **13** when 1.5 equiv of reagent was utilized (Scheme 2). Under the same conditions, chloropyridone **3** was obtained with 74% yield after only one night (Scheme 1).

It was evidently not expected that fluorination could be realized by using these methods. Nevertheless, when benzodioxole **6** was subjected to 40% HF/*iso*-amyl nitrite/CH_2Cl_2 for 3 days, 4-nitrobenzodioxole **14** was formed in 80% NMR yield (Scheme 3). Even by using only a few amount of *iso*-amyl nitrite, we were not able to observe the possible nitroso intermediate **15** that was oxidized in situ to give **14**.

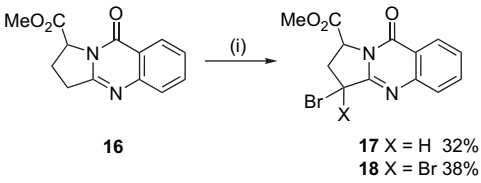
2.4. Other reactions of the HBr/*iso*-amyl nitrite system and possible mechanisms

Some other bromination reactions were performed with this system, which allowed suggesting a part of the reaction mechanism.



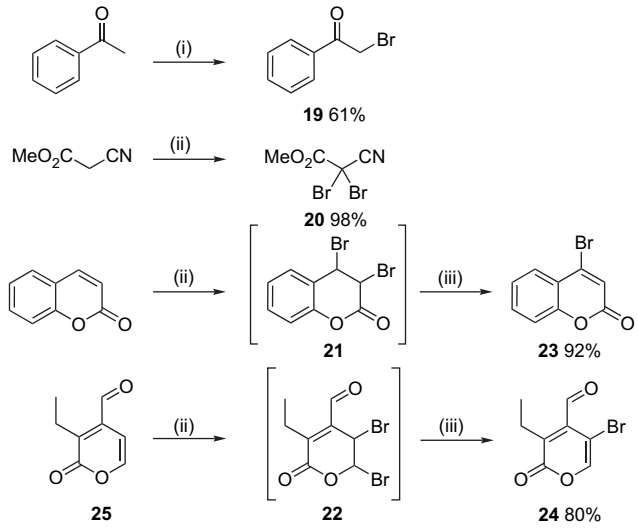
Scheme 3. Reaction conditions: (i) *iso*-amyl nitrite (2 equiv), 40% HF (3 equiv), CH_2Cl_2, 20 °C, 3 days.

Indeed, no bromination occurred when HBr was changed for KBr. Thus, an initial oxidation of Br^- by *iso*-amyl nitrite to give Br^+ then Br_2 can be excluded. Another possibility is formation of nitrous acid and *iso*-amyl bromide. This can then react either as a bromonium ion source or give the radical Br•. Moreover, by using a Dräger tube, it was observed that the brown vapours formed in the beginning of the reaction are not bromine or chlorine. In the same way as for analogue reactions,[22] the absence of halogenation of the methyl group of toluene (Table 2, entry 2) is indicative for an electrophilic mechanism of the reaction more than a radical pathway. However, this needs to be nuanced because when heterocycle **16**[34] was subjected to the reaction, a mixture of mono and dibrominated products **17** and **18** was obtained in 70% yield (Scheme 4).



Scheme 4. Reaction conditions: (i) *iso*-amyl nitrite (3 equiv), 48% HBr (0.9 equiv), CH_2Cl_2, 20 °C, 12 h.

There are many differences in the kinetics and regioselectivity between this bromination of arenes and the one realized with free bromine. Thus, it is likely that the postulated *iso*-amyl bromide reacted as a Br^+ cation equivalent. The following reactions go in the same direction: α-bromination of acetophenones in dioxane, with HBr and TBHP[22] at 60 °C, or with H_2O_2 at reflux[35] has been described in literature; in the latter, a mixture containing mainly the dibromoketone was formed, and the reaction was thought to process from the enol form of the ketone.[35] The new HBr/*iso*-amyl nitrite system led to 61% of α-bromoacetophenone **19** in 48 h at room temperature (Scheme 5). In the same way, methyl cyanomalonate yielded quantitatively to dibromo product **20**. A possible mechanism is the formation of a cyclic bromonium ion



Scheme 5. Reaction conditions: (i) *iso*-amyl nitrite (2 equiv), HBr (1.5 equiv), 48 h, rt; (ii) *iso*-amyl nitrite (3 equiv), HBr (2 equiv), 48 h, rt; (iii) DBU (1.5 equiv), CH_2Cl_2, 1 h, rt.

intermediate on the double bond of enolized carbonyl compounds, followed by attack of unoxidized bromide ion and then elimination of HBr. That is comforted by the formation of dibromocoumarine **21** and dibromopyranone **22** (characterized by ^{1}H NMR) from the corresponding heterocycles. These compounds were not purified but subjected to the action of DBU to give 92% of bromocoumarine **23** and 80% of **24**. It is important to note that direct addition of bromine on aldehyde **25**[36] led to complex mixture from which, according to ^{1}H NMR, only few amount of **22** formed, pointing against formation of Br_2 from the HBr/*iso*-amyl nitrite mixture.

3. Conclusion

We have presented our results towards an environmentally safe procedure for the bromination of different compounds using a simple reaction protocol. The positive bromine reagent is prepared in situ from aqueous hydrobromic acid and *iso*-amyl nitrite as oxidant. The method is practically feasible, and safer than bromination with molecular bromine.

4. Experimental section

4.1. General

Melting points were determined using an Electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. IR spectra were obtained in ATR mode on a FTIR Bruker Tensor 27. Thin layer chromatographies were performed on precoated Kieselgel 60F_{254} plates. APCI$^+$ (atmospheric pressure chemical ionization) mass spectra were obtained on an LC–MS system Thermo Electron Surveyor MSQ. Microanalyses were performed by the 'Service de Microanalyses' of LSEO, Université de Bourgogne, Dijon, France. All products are obtained as mixtures of diastereoisomers.

4.2. Dimethyl 6-chloro-7-methoxycarbonylmethyl-5-oxo-1,2,3,5-tetrahydro-indolizine-3,8-dicarboxylate (3)

A mixture of **1** (0.21 g, 0.65 mmol), and *iso*-amyl nitrite (0.3 mL, 2.23 mmol) in 37% hydrochloric acid (0.1 mL, 0.78 mmol) and tetrahydrofuran (3 mL) was stirred at room temperature for 15 h. The mixture was extracted with dichloromethane (2×50 mL). The combined organic layers were dried (sodium sulfate), filtered and evaporated. The residue was then subjected to flash chromatography (ethyl acetate/heptane, 70/30) to give **3**. Yellow oil; 74% yield; TLC R_f (AcOEt)=0.65; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 2.22–2.64 (m, 2H, CH_2CH_2CH), 3.43–3.56 (m, 2H, CH_2CH_2CH), 3.72 (s, 3H, CO_2CH_3), 3.80 (s, 3H, CO_2CH_3), 3.82 (s, 3H, CO_2CH_3), 4.14 (s, 2H, CH_2), 5.19 (dd, J=9.5, 3.2 Hz, 1H, CH_2CH_2CH); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ 28.4 (CH_2), 36.2 (CH_2), 40.6 (CH_2), 54.9 (CH_3), 55.1 (CH_3), 55.9 (CH_3), 56.3 (CH), 65.6 (C), 110.1 (C), 128.2 (C), 146.3 (C), 156.8 (C), 159.4 (C), 168.1 (C), 172.5 (C); IR: ν cm^{-1} 1750, 1720, 1670, 1580, 1520, 1440, 1200. Anal. Calcd for $C_{15}H_{16}ClO_7N$: C, 50.26; H, 4.51; N, 3.92. Found: C, 49.94; H, 4.61; N; 3.86.

4.3. Dimethyl 6-bromo-7-methoxycarbonylmethyl-5-oxo-1,2,3,5-tetrahydro-indolizine-3,8-dicarboxylate (5)

Pyridone **1** (300 mg, 0.92 mmol) was dissolved in 1 mL of dichloromethane. A solution of aq 48% HBr (1.3 mmol, 0.16 mL) was added followed by *iso*-amyl nitrite (1.8 mmol, 0.1 mL). The reaction mixture was stirred at room temperature for necessary time (Table 2), then aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with dichloromethane (2×10 mL). The combined organic layers were dried and then evaporated. White powder; 98% yield; TLC R_f (heptane/AcOEt: 50/50)=0.2; mp (AcOEt) 110 °C; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 2.18–2.60 (m, 2H, CH_2CH_2CH), 3.36–3.49 (m, 2H, CH_2CH_2CH), 3.67 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 4.12 (s, 2H, CH_2), 5.12 (dd, J=9.7, 3.2 Hz, 1H, CH_2CH_2CH); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ 25.4 (CH_2), 33.2 (CH_2), 37.6 (CH_2), 51.8 (CH_3), 52.1 (CH_3), 52.8 (CH_3), 53.3 (CH_3), 62.6 (CH), 107.0 (C), 125.2 (C), 143.3 (C), 153.8 (C), 156.4 (C), 165.1 (C), 169.5 (C); IR: ν cm^{-1} 1740, 1730, 1720, 1590, 1500, 1430, 1200. Anal. Calcd for $C_{15}H_{16}BrO_7N$: C, 44.80; H, 4.01; N, 3.48. Found: C, 44.97; H, 4.19; N; 3.44.

4.4. General procedure of oxybromination

Arene (5 mmol) was dissolved in 5 mL of dichloromethane. A solution of aq 48% HBr (7.5 mmol, 0.85 mL) was added followed by *iso*-amyl nitrite (10 mmol, 0.4 mL). The reaction mixture was stirred at room temperature for necessary time then aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with dichloromethane (2×10 mL). The combined organic layers were dried then evaporated. The crude products were identified according to the ^{1}H NMR spectra of pure compounds, or from literature data.

4.4.1. 5-Bromo-1,3-benzodioxole

Yield 100%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.95 (s, 2H, CH_2), 6.66 (d, J=8.8 Hz, 1H, Ar*H*), 6.92 (m, 2H, Ar*H*).

4.4.2. 1-Bromo-4-methylbenzene

Yield 67%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.28 (s, 3H, CH_3), 7.02 (d, J=8.1 Hz, 2H, Ar*H*), 7.37 (d, J=8.4 Hz, 2H, Ar*H*).

4.4.3. 1-Bromo-2-methylbenzene

Yield 17%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.38 (s, 3H, CH_3), 7.04 (m, 1H, Ar*H*), 7.13–7.22 (m, 2H, Ar*H*), 7.48–7.52 (m, 1H, Ar*H*).

4.4.4. 1-Bromonaphthalene

Yield 85%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.24 (t, J=8.1 Hz, 1H, Ar*H*), 7.42–7.57 (m, 2H, Ar*H*), 7.71–7.79 (m, 3H, Ar*H*), 8.2 (d, J=8.4 Hz, 1H, Ar*H*).

4.4.5. 2,4-Dibromo-1-naphthol

Yield 70%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.56 (m, 1H, Ar*H*), 7.92 (s, 1H, Ar*H*), 8.44–8.51 (m, 1H, Ar*H*), 8.8–8.85 (m, 1H, Ar*H*).

4.4.6. 2-Bromo-1-phenylethanone

Yield 61%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.48 (s, 2H, CH_2Br), 7.45–7.67 (m, 3H, Ar*H*), 7.95–8.04 (m, 2H, Ar*H*).

4.4.7. Methyl dibromo(cyano)acetate

Yield 98%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.02 (s, 3H, CO_2CH_3).

4.5. Dimethyl 7-(1-(methoxycarbonyl)propyl)-1,2,3,5-tetrahydro-6-bromo-5-oxoindolizine-3,8-dicarboxylate (9)

Pyridone **8** (1.5 g, 4.4 mmol) was dissolved in 44 mL of dichloromethane. Solution of aq 48% HBr (0.75 mL, 6.6 mmol) was added follow by *iso*-amyl nitrite (1.22 mL, 8.8 mmol). The reaction mixture was stirred at room temperature for 6 h, and then aqueous $NaHCO_3$ (60 mL) was added and the mixture was extracted by dichloromethane (2×100 mL). The combined organic layers were dried then evaporated. The residue was purified by chromatography on SiO_2 (heptane/EtOAc, 100/0% to 0/100%), to give compound **9**. Yellow oil; 98% yield; TLC R_f (AcOEt)=0.5; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.95, 0.97 (2t, J=7.4 Hz and J=8.2 Hz, 3H, $CHCH_2CH_3$), 1.50–1.75 (m, 1H, $CHCH_2CH_3$), 2.24–2.63 (m, 3H, $CHCH_2CH_3$ and CH_2CH_2CH), 3.36–3.54 (m, 2H, CH_2CH_2CH), 4.43, 4.45 (2d, J=8.2 Hz and J=7.2 Hz, 1H, $CHCH_2CH_3$), 5.17, 5.19 (2dd, J=9.7, 5.8 Hz and J=9.6, 5.4 Hz, 1H, CH_2CH_2CH); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ 10.9

(CH_3), 22.1 (CH_2), 23.9 (CH_2), 31.1 (CH_2), 50.2 (CH_3), 50.3 (CH_3), 50.7 (CH), 51.3 (CH_3), 61.2 (CH), 105.5 (C), 117.0 (C), 148.8 (C), 152.2 (C), 155.2 (C), 163.8 (C), 168.0 (C), 170.1 (C); IR: ν cm^{-1} 1738, 1719, 1654, 1436, 1259, 1209. Anal. Calcd for $C_{17}H_{20}BrNO_7$: C, 47.46; H, 4.69; N, 3.26. Found: C, 47.25; H, 4.77; N; 3.20.

4.6. Methyl 6,8-dibromo-7-[1-(methoxycarbonyl)propyl]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (11)

The pyrrolopyridone **10** (600 mg, 2 mmol) was dissolved in 10 mL of dichloromethane. Solution of aq 48% HBr (6 mmol, 0.7 mL) was added followed by *iso*-amyl nitrite (4 mmol, 0.9 mL). The reaction mixture was stirred at room temperature for 6 h then aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted by dichloromethane (2×20 mL). The combined organic layers were dried then evaporated. The product was isolated by crystallization and recrystallized in a mixture of ethyl acetate and ether. Yellow powder; 84% yield; TLC R_f (AcOEt)=0.7; mp (AcOEt) 69–70 °C; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.97, 0.98 (2t, J=7.3 Hz and J=7.3 Hz, 3H, $CHCH_2CH_3$), 1.87–2.15 (m, 2H, $CHCH_2CH_3$), 2.25–2.7 (m, 2H, CH_2CH_2CH), 3.15–3.27 (m, 2H, CH_2CH_2CH), 3.7(s, 3H, CO_2CH_3), 3.82, 3.83 (2s, 3H, CO_2CH_3), 4.27–4.46 (br s, 1H, $CHCH_2CH_3$), 5.24, 5.25 (2dd, J=9.5, 3.5 Hz and J=9.5, 3.3 Hz, 1H, CH_2CH_2CH); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ 11.9 (CH_3), 22.5 (CH_2), 25.4 (CH_2), 33.7 (CH_2), 52.5 (CH, CH_3), 53.9 (CH_3), 64.1 (CH), 148.9 (C), 150.4 (C), 156.5 (C), 168.0 (C), 169.7 (C), 171.4 (C); IR: ν cm^{-1} 1738, 1729, 1642, 1590, 1549, 1530, 1204. Anal. Calcd for $C_{15}H_{17}Br_2O_5N\cdot{}^1/_2\ H_2O$: C, 39.16; H, 3.94; N, 3.04. Found: C, 39.31; H, 3.81; N; 3.16.

*4.6.1. Methyl 8-bromo-7-[1-(methoxycarbonyl)propyl]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**12**)*

The pyrrolopyridone **10** (600 mg, 2 mmol) was dissolved in 10 mL of dichloromethane. Solution of aq 48% HBr (6 mmol, 0.7 mL) was added followed by *iso*-amyl nitrite (4 mmol, 0.9 mL). The reaction mixture was stirred at room temperature for 6 h then aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted by dichloromethane (2×20 mL). The combined organic layers were dried then evaporated. The residue was purified by chromatography on SiO_2 (heptane/EtOAc, 100/0% to 0/100%). Yellow oil; 78% yield; TLC R_f (AcOEt)=0.6; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.96, 0.98 (2t, J=7.4 and J=7.3 Hz, 3H, $CHCH_2CH_3$), 1.66–2.14 (m, 2H, $CHCH_2CH_3$), 2.24–2.67 (m, 2H, CH_2CH_2CH), 3.16–3.26 (m, 2H, CH_2CH_2CH), 3.70, 3.71 (2s, 3H, CO_2CH_3), 3.75 (m, 1H, $CHCH_2CH_3$), 3.80, 3.81 (2s, 3H, CO_2CH_3), 5.19 (dd, J=9.7, 3.4 Hz, 1H, CH_2CH_2CH), 6.43 (s, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ 11.0 (CH_3), 25.3 (CH_2), 25.6 (CH_2), 33.0 (CH_2), 51.0 (CH), 52.2 (CH_3), 52.5 (CH_3), 62.7 (CH), 97.5 (C), 116.9 (CH), 148.0 (C), 151.9 (C), 160 (C), 170 (C), 172 (C); IR: ν cm^{-1} 1738, 1670, 1596, 1533, 1438, 1339, 1210. Anal. Calcd for $C_{15}H_{18}BrNO_5$, H_2O: C, 46.17; H, 5.17; N, 3.59. Found: C, 46.58; H, 4.85; N, 3.82.

4.7. Dimethyl 7-(1-(methoxycarbonyl)propyl)-1,2,3,5-tetrahydro-6-chloro-5-oxoindolizine-3,8-dicarboxylate (13)

A solution of **8** (300 mg, 0.85 mmol) in THF (4 mL), 37% hydrochloric acid (0.1 mL, 1.16 mmol) and *iso*-amyl nitrite (0.4 mL, 2.89 mmol) was stirred at room temperature for 1 week. The mixture was neutralized by satd aqueous $NaHCO_3$ (50 mL) and the aqueous phase was extracted with dichloromethane (3×30 mL) and the combined organic layers were dried ($MgSO_4$) then evaporated. The residue was purified by chromatography on SiO_2 (heptane/EtOAc, 100/0% to 0/100%) to give compound **14**. Yellow oil; 60% yield; TLC R_f (AcOEt)=0.6; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.94, 0.95 (2t, J=7.3 and J=7.4 Hz, 3H, $CHCH_2CH_3$), 1.52–1.83 (m, 1H, $CHCH_2CH_3$), 2.25–2.65 (m, 3H, $CHCH_2CH_3$ and $CH_2CH_2CH_3$), 3.39–3.51 (m, 2H, CH_2CH_2CH), 3.66 (m, 3H, CO_2CH_3), 3.79, 3.8 (2s, 3H, CO_2CH_3), 3.81, 3.82 (2s, 3H, CO_2CH_3), 4.42, 4.43 (2dd, J=8, 3.6 Hz and J=8.2, 3.7 Hz, 1H, $CHCH_2CH_3$), 5.14–5.23 (m, 1H, CH_2CH_2CH); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ 12.4 (CH_3), 23.4 (CH_2), 25.6 (CH_2), 32.8 (CH_2), 49.1 (CH), 51.8 (CH_3), 51.9 (CH_3), 52.9 (CH_3), 62.6 (CH), 106.8 (C), 125.3 (C), 148 (C), 153 (C), 156.6 (C), 165.4 (C), 169.6 (C), 171.8 (C); IR: ν cm^{-1} 1738, 1717, 1654, 1432, 1262, 1209. Anal. Calcd for $C_{17}H_{20}ClNO_7$: C, 52.93; H, 5.23; N, 3.63. Found: C, 53.08; H, 5.34; N, 3.81.

4.8. 5-Nitro-1,3-benzodioxole (14)

To a stirred solution of arene (5 mmol) and aq solution of HF 40% (0.6 mL, 15 mmol) in a Teflon flask was added *iso*-amyl nitrite (2 mmol, 0.4 mL). The mixture was stirred at room temperature for 3 days and the solvent was evaporated. The residue was diluted with dichloromethane (10 mL) and washed with satd aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with dichloromethane (2×10 mL) and the combined organic layers were dried ($MgSO_4$). The residue obtained upon evaporation was analyzed by ^{1}H NMR and identified according to the literature data. 80% yield; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 3.97, 3.99 (2s, 6H, OCH_2O), 6.93 (d, J=8.9 Hz, 1H, Ar*H*), 7.75 (d, J=2.7 Hz, 1H, Ar*H*), 7.92 (dd, J=8.9, 2.7 Hz, 1H, Ar*H*).

4.9. Brominated pyrroloquinazolinones

To a solution of compound **16** (1.0 g, 4.1 mmol) in dichloromethane (10 mL) were slowly added *iso*-amyl nitrite (1.6 mL, 8.0 mmol), then a solution of aq 48% HBr (1 mL, 3.6 mmol). The reaction mixture was stirred at room temperature for 12 h. A saturated aqueous solution of $NaHCO_3$ was then added, and the mixture was extracted with dichloromethane. The combined organic layers were washed with water, then dried upon $MgSO_4$ and evaporated. The dark residue was then separated by HPLC using a gradient of ethyl acetate in heptane to yield to cis and trans monobrominated products **17** and dibrominated product **18**.

*4.9.1. Methyl 3-bromo-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (**17**)*

4.9.1.1. Cis isomer. Grey powder; 10% yield; mp 124–126 °C; TLC R_f (EtOAc/Hept 50/50)=0.26; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 2.92 (dt, J=15.2, 1.5 Hz, 1H, CH–CH_2–CHBr), 3.20 (ddd, J=15.2, 9.4, 7.2 Hz, 1H, CH–CH_2–CHBr), 3.84 (s, 3H, CO_2CH_3), 5.22 (dd, J=7.2, 1.5 Hz, 1H, CH–CH_2–CHBr), 5.29 (dd, J=9.4, 1.5 Hz, 1H, CH–CH_2–CHBr), 7.54 (dd, J=8.0, 6.1 Hz, 1H, *H*ar), 7.79 (d, J=8.2 Hz, 1H, *H*ar), 7.81 (ddd, J=8.2, 6.1, 1.5 Hz, 1H, *H*ar), 8.33 (ddd, J=8.0, 1.5, 0.7 Hz, 1H, *H*ar); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 28.7 (CH_2), 41.6 (CH_3), 52.2 (CH), 56.7 (CH), 119.9 (C), 125.8 (CH), 126.6 (CH), 126.9 (CH), 133.8 (CH), 147.8 (C), 155.7 (C),158.9 (C), 167.8 (C); IR: ν cm^{-1} 1751, 1667, 1631, 1214, 695; ^{1}H NMR ($CDCl_3$, 200 MHz). Anal. Calcd for $C_{13}H_{11}BrN_2O_3\cdot{}^3/_4\ H_2O$: C, 46.38; H, 3.74; N, 8.32. Found: C, 46.06; H, 3.79; N, 8.67.

4.9.2. Trans isomer

Grey powder; 22% yield; mp 132–134 °C; TLC R_f (EtOAc/Hept 50/50)=0.41; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.91 (dd, J=7.2, 5.8 Hz, 2H, CH–CH_2–CHBr), 3.85 (s, 3H, CO_2CH_3), 5.17 (t, J=7.2 Hz, 1H, CH–CH_2–CHBr), 5.34 (t, J=7.2 Hz, 1H, CH–CH_2–CHBr), 7.52 (ddd, J=7.9, 7.2, 1.9 Hz, 1H, *H*ar), 7.78 (dd, J=8.3, 1.9 Hz, 1H, *H*ar), 7.80 (ddd, J=8.3, 7.2, 1.1 Hz, 1H, *H*ar), 8.29 (ddd, J=7.9, 1.1 Hz, 1H, *H*ar); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 28.7 (CH_2), 41.6 (CH_3), 52.2 (CH), 56.7 (CH), 119.9 (C), 125.8 (CH), 126.6 (CH), 126.9 (CH), 133.8 (CH), 147.8 (C), 155.7 (C),158.9 (C), 167.8 (C); IR: ν cm^{-1} 1751, 1667, 1631, 1214, 695. Anal. Calcd for $C_{13}H_{11}BrN_2O_3\cdot{}^3/_4\ H_2O$: C, 46.38; H, 3.74; N, 8.32. Found: C, 46.22; H, 3.72; N, 8.02.

4.10. Methyl 3,3-dibromo-9-oxo-1,2,3,9-tetrahydropyrrolo-[2,1-*b*]quinazoline-1-carboxylate (18)

Grey crystals; 38% yield; mp (AcOEt) 128–130 °C; TLC R_f (EtOAc/Hept 60/40)=0.7; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.55 (dd, J=14.8, 4.6 Hz, 1H, CH–C*H*$_2$–CBr_2), 3.69 (dd, J=14.8, 7.8 Hz, 1H, CH–C*H*$_2$–CBr_2), 3.86 (s, 3H, CO_2CH_3), 5.15 (dd, J=7.8, 4.6 Hz, 1H, C*H*–CH_2–CBr_2), 7.57 (ddd, J=7.9, 6.6, 1.7 Hz, 1H, *H*ar), 7.84 (ddd, J=8.2, 6.6, 1.5 Hz, 1H, *H*ar), 7.92 (ddd, J=8.2, 1.7, 0.7 Hz, 1H, *H*ar), 8.32 (ddd, J=7.9, 1.5, 0.7 Hz, 1H, *H*ar); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 49.3 (CH_2), 53.2 (CH_3), 55.8 (CH), 62.3 (C), 120.5 (C), 126.6 (CH), 127.9 (CH), 128.1 (CH), 134.8 (CH), 148.3 (C), 155.5 (C), 159.3 (C), 167.6 (C); IR: ν cm^{-1} 1747, 1680, 1616, 1224, 693. Anal. Calcd for $C_{13}H_{10}Br_2N_2O_3 \cdot {}^1/_2\ H_2O$: C, 37.99; H, 2.70; N, 6.82. Found: C, 37.92; H, 2.78; N, 6.80.

4.11. Bromination of coumarine or pyranone 25

Coumarine or pyranone **25** (1.1 mmol) was dissolved in 3 mL of dichloromethane. A solution of aq 48% HBr (2 mmol, 0.23 mL) was added followed by *iso*-amyl nitrite (3.2 mmol, 0.72 mL). The reaction mixture was stirred at room temperature for 2 days giving dibromo intermediate.

*4.11.1. 3,4-Dibromochroman-2-one (**21**)*

^{1}H NMR: ($CDCl_3$, 200 MHz) δ 4.97 (d, J=2.5 Hz, 1H, C*H*Br), 5.35 (d, J=2.5, 1H, C*H*Br), 7.15–7.29 (m, 2H, Ar*H*), 7.36–7.51 (m, 2H, Ar*H*).

*4.11.2. 2,3-Dibromo-5-ethyl-6-oxo-3,6-dihydro-2H-pyran-4-carbaldehyde (**22**)*

^{1}H NMR: ($CDCl_3$, 200 MHz) δ 1.28 (q, J=7.4 Hz, 3H, CH_2CH_3), 2.94 (t, J=7.4 Hz, 2H, CH_2CH_3), 5.33 (d, J=1.5 Hz, 1H, C*H*Br), 6.77 (s, J=1.5 Hz, 1H, C*H*Br), 10.25 (s, 1H, C*H*O).

DBU (1.6 mmol, 0.3 mL) was added and the reaction mixture was stirred for 1 h. Solvents were then evaporated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and washed with distilled water (2×50 mL). The combined organic layers were dried (Na_2SO_4) and then evaporated.

*4.11.3. 4-Bromo-2H-chromen-2-one (**23**)*

Yield 92%; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 7.26–7.39 (m, 2H, Ar*H*), 7.45–7.64 (m, 2*H*, Ar*H*), 8.13 (s, 1H, Ar*H*).

*4.11.4. 5-Bromo-3-ethyl-2-oxo-2H-pyran-4-carbaldehyde (**24**)*

Yellow oil; 80% yield; TLC R_f (AcOEt)=0.6; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 1.21 (t, J=7.4 Hz, 3H, CH_2CH_3), 2.72 (q, J=7.4 Hz, 2H, CH_2CH_3), 7.6 (s, 1H, Ar*H*), 10.18 (s, 1H, CO*H*).

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