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SYNTHESIS OF NEW 3-NITROIMIDAZO[1,2-*a*]PYRIDINE DERIVATIVES BY S_{RN}1 REACTIONS

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Abstract – 6,8-Dibromo-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine was prepared and reacted under experimental conditions of S_{RN}1 reactions with different carbon and sulfur centered nucleophiles to determine the relative reactivities of the different types of electrophile halides. Depending on the nucleophile nature, the chloromethyl group and bromine atom in 8-position were found to be reacting under these experimental conditions. An S_{RN}1 reaction on the pyridine part of the imidazo[1,2-*a*]pyridine is described for the first time.

INTRODUCTION

Imidazo[1,2-*a*]pyridine derivatives are currently the object of a renewed interest in the pharmacological field.^{1,2} Many recent publications report their pharmacological activities in various biological areas. For example, gastric antisecretory,³ local anesthetic,⁴ antiviral,⁵ hypnotic^{6,7} and anxiolytic⁸ properties have been described. It is particularly in the field of the central nervous system that the activity of this skeleton appears to have currently the most importance, contributing in particular to a better comprehension of the mechanism of action of psychotropic drugs.⁹

Unimolecular radical nucleophilic substitution (S_{RN}1) has been found to be an excellent method for many types of aromatic, heterocyclic and aliphatic substrates with suitable leaving groups.^{10,11} In continuation of our study of the reactivity in 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine series in electron transfer reactions¹²⁻¹³ and as part of a program directed to the preparation of more complex structures of pharmacological interest,¹⁴⁻¹⁶ we have prepared 6,8-dibromo-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine and studied their reactivity with different nucleophiles under S_{RN}1 experimental conditions, in order to determine the relative reactivity of the different electrophile halides.

RESULTS AND DISCUSSION

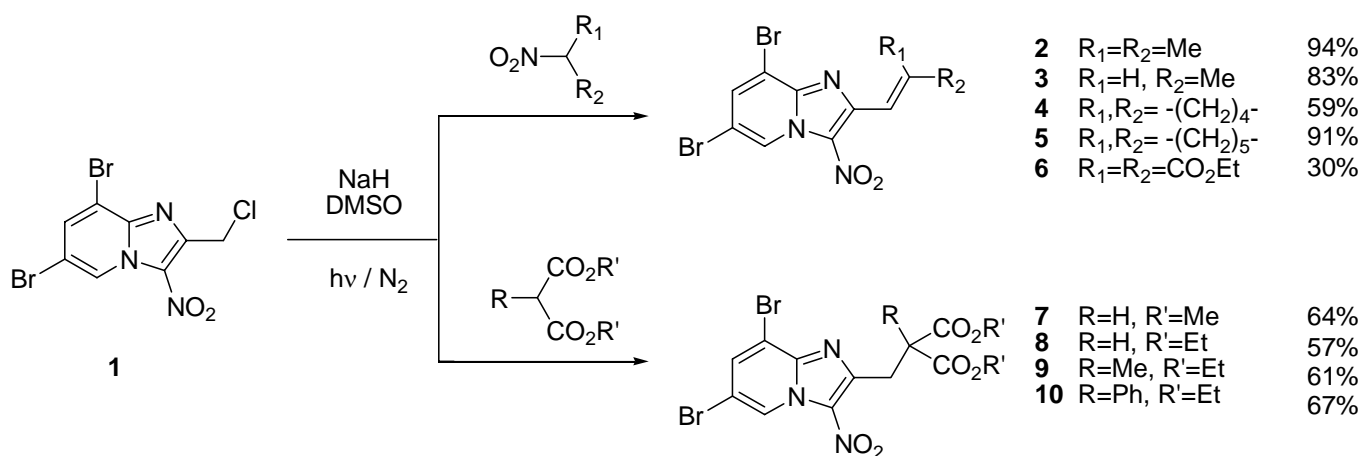
The starting material **1** was easily obtained by condensation of commercial 2-amino-3,5-dibromopyridine with 1,3-dichloroacetone in ethanol to give 6,8-dibromo-2-chloromethylimidazo[1,2-*a*]pyridine which was nitrated with 65% nitric acid at the 3-position.¹⁶ In $S_{RN}1$ experimental conditions, the nitronate, malonate (Scheme 1, Table 1) and sulfinate (Scheme 2, Table 3) anions react only on the chloromethyl group at the 2-position of the 6,8-dibromo-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine (**1**) in DMSO under nitrogen with photostimulation to give the corresponding products in moderate yields (30-94 %).

The reactions with *C*-centered nucleophile anions were performed using 3 equivalents of nitroalkane or malonate derivatives in DMSO. In order to form the corresponding carbanions, we used 60% NaH in DMSO.¹⁷

In agreement with previous works, photoinduced consumption of substrate (**1**) by various anions increased in DMSO.¹⁸ Furthermore, solvation effects have been shown with dipolar aprotic solvents that can exert a strong influence on formation and reactivity of radical anions.

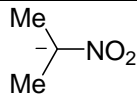
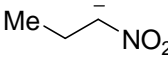
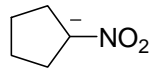
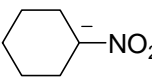
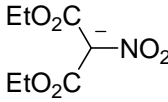
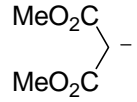
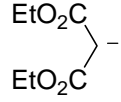
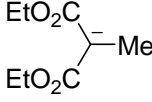
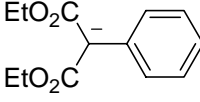
Under $S_{RN}1$ experimental conditions (inert atmosphere, photostimulation), the reaction with nitroalkane anions gave the ethylenic derivatives (**2-6**) resulting from the consecutive *C*-alkylation and nitrous acid elimination from *C*-alkylated product.

Scheme 1



In order to confirm the single electron transfer in the reaction of **1** with 2-nitropropane or diethyl phenylmalonate sodium salts, we added classical inhibitors¹⁹ (TEMPO and CuCl₂) and we have compared the reaction rates (Table 2). For a coherent comparison, reaction times were identical for inhibition study and corresponded to the optimized conditions without inhibitor. These reactions are strongly inhibited in presence of TEMPO, a classical free radical scavenger used in the mechanism studies of $S_{RN}1$ reaction.¹⁹

Table 1. Reaction with various C-centered anions

Entry	Anions	Time	Yield (%)	Product
1		20 min	94	2
2		35 min	83	3
3		15 min	59	4
4		20 min	91	5
5		28 h	30	6
6		10 min	64	7
7		15 min	57	8
8		15 min	61	9
9		15 min	67	10

Furthermore, ligand transfer oxidation by cupric salts with radical suppressed carbon alkylation.

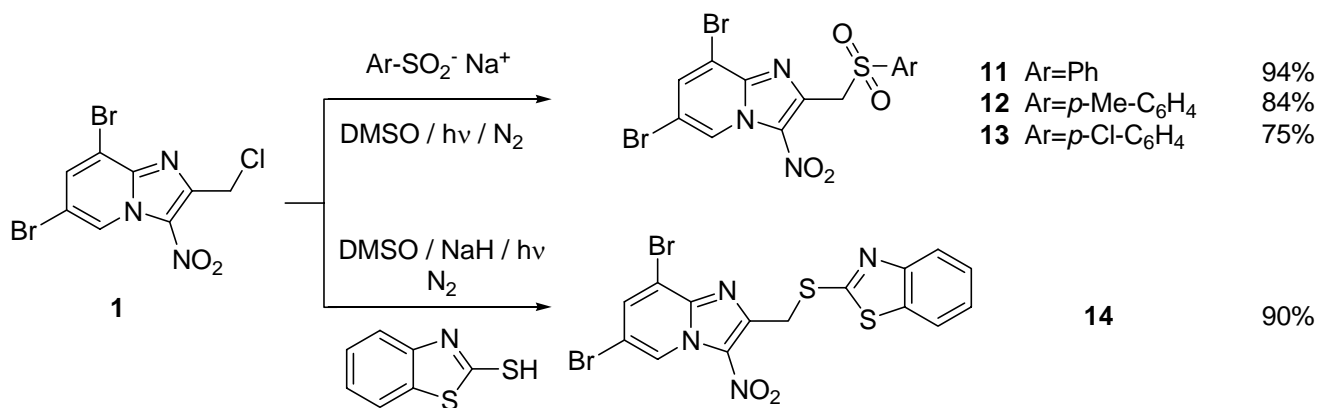
As an understanding of the relationship between the nucleophile and the substrate in single electron transfer is useful in order to increase the selectivity and the yield of the reaction,²⁰ we have investigated the reactivity of **1** with other conventional nucleophiles as for example S-centered anions²¹ (Table 3). The reaction between the sodium salt of arylsulfonic acids (Entries 14-16) or 2-sulfanylbenzothiazole (BzTh-SH, entry 18) in DMSO gave the required products in good to excellent yields (75-94 %, Scheme 2, Table 3) only by replacement of chlorine atom.

In order to identify the main mechanism of the reaction, we have studied the reactivity of this last reaction by addition of cupric chloride as inhibitor (Table 3, entry 16).²² When this last inhibitor is added in catalytic quantity to the reaction mixture, the yield of **12** strongly decreased. This indicates that the rate of reaction is retarded and the reaction does not stop.

Table 2. Reaction with various C-centered anions

Entry	Anions	Inhibitor	Time	Yield (%)	Product
10		CuCl ₂	20 min	10	2
11		TEMPO	20 min	0	2
12		CuCl ₂	15 min	13	10
13		TEMPO	15 min	0	10

Furthermore, the reaction does not follow free radical chain mechanism exclusively, rather, both the mechanisms with free radical chain and nucleophilic substitution displacement reaction are operative.

Scheme 2**Table 3.** Reaction with various S-centered anions

Entry	Anions	Conditions	Time	Yield (%)	Product
14	Ph-SO ₂ ⁻ Na ⁺	DMSO	2 h	94	11
15	<i>p</i> -Me-C ₆ H ₄ -SO ₂ ⁻ Na ⁺	DMSO	2 h	84	12
16	<i>p</i> -Me-C ₆ H ₄ -SO ₂ ⁻ Na ⁺	DMSO / 10% CuCl ₂	2 h	57	12
17	<i>p</i> -Cl-C ₆ H ₄ -SO ₂ ⁻ Na ⁺	DMSO	2 h	75	13
18	BzTh-SH	DMSO / NaH	20 min	90	14

Moreover, thiophenol presented noteworthy reactivity (Scheme 3 and Table 4, entry 19). Actually, treating **1** with 2.2 or even 1.2 equivalents of thiophenol and equimolar amount of NaH in DMSO resulted in 6-bromo-3-nitro-8-phenylsulfanyl-2-phenylsulfanylmethylimidazo[1,2-*a*]pyridine (**15**), from concomitant replacement of bromine atom at the 8-position and chlorine atom on the chloromethyl group at the 2-position, as main product. The structure of **15** was confirmed by X-ray analysis (Figure 1).

Scheme 3

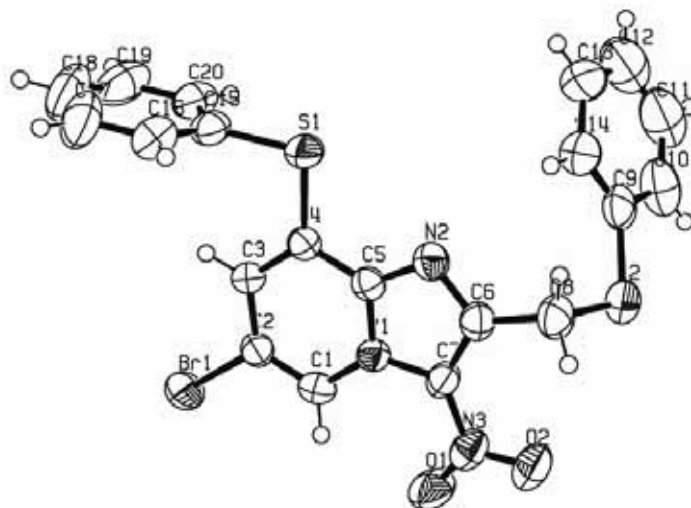
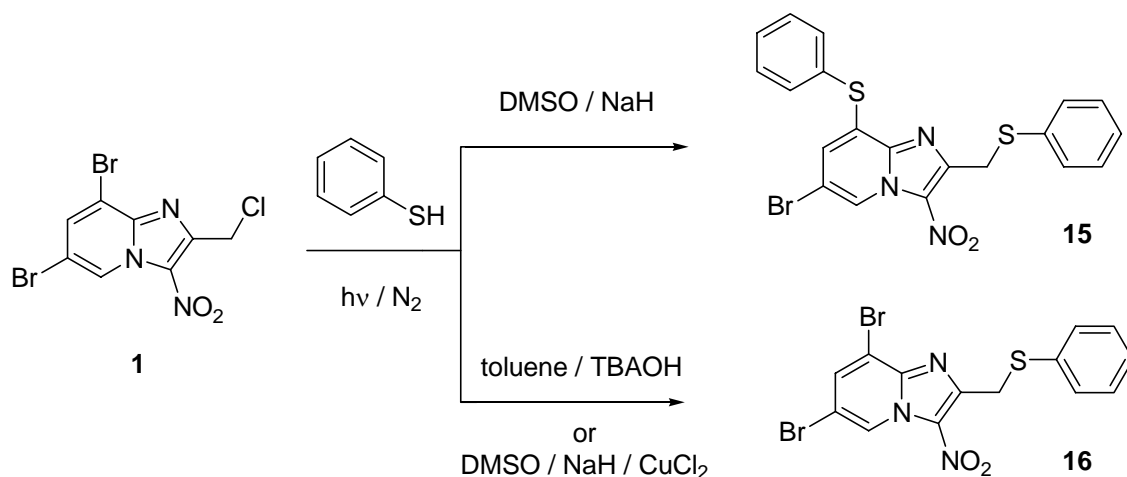


Figure 1. ORTEP plot of the 6-bromo-3-nitro-8-phenylsulfanyl-2-phenylsulfanylmethylimidazo[1,2-*a*]pyridine (**15**).

Table 4. Reaction with thiophenol

Entry	Anion	Conditions	Time	Yield (%)	Product
19	Ph-SH	DMSO / NaH	25 min	71	15
20	Ph-SH	toluene / TBAOH	4 h	63	16
21	Ph-SH	DMSO / NaH / 10% CuCl ₂	25 min	67	16

As already described, the 8-position of imidazo[1,2-*a*]pyridine could react with alcoholate, thiolate anions or hydrogen sulfide but the mechanism was not clearly established.^{7,23} Indeed, the reaction may be thought to proceed through either of the two mechanisms (i) a simple nucleophilic aromatic substitution (S_NAr) or (ii) a free radical chain mechanism ($S_{RN}1$). However, mechanism in benzene, naphthalene or heterocyclic (pyridine, quinoline, thiophene) series was clearly studied with brominated or iodinated compounds and followed single electron transfer reaction.²⁴ In order to identify the main mechanism of the reaction, we have studied the reactivity by addition of $CuCl_2$ as inhibitor.

The constatations observed with sulfinate anions are applicable to the reactivity between compound **1** and phenylthiolate anion but only with the chloromethyl group at 2-position (Scheme 3). Indeed, when the inhibitor is added to the reaction mixture, only the reactivity at 8-position is stopped. By contrast, the reaction of the chloromethyl group is slightly retarded when inhibitor was added. These observations could suggest that the 8-position reacts only *via* free radical chain reaction, and the chloromethyl group at 2-position could follow a borderline mechanism, between S_N2 and $S_{RN}1$.

In conclusion, the 6,8-dibromo-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine reacts with different carbon and sulfinate centered anions only by substitution of chloromethyl group. The reaction is very probably mediated by an $S_{RN}1$ mechanism. Furthermore, with phenylthiolate anion we found a double reactivity at the 8-position and chloromethyl group. The reaction at the 8-position followed very certainly an electron transfer process on the other hand the chloromethyl group could not follow free radical chain mechanism exclusively.

This regioselectivity in imidazo[1,2-*a*]pyridine series is described for the first time in the literature and could be used for the preparation of more complexe structures of pharmacological interest. Work is under progress to prepare new derivatives by $S_{RN}1$ reaction on the pyridine moiety.

EXPERIMENTAL

General Methods. Melting points were determined with a B-540 Büchi melting point apparatus. 200 MHz 1H NMR and 50 MHz ^{13}C NMR spectra were recorded on a Bruker ARX 200 spectrometer in $CDCl_3$ or $DMSO-d_6$ solution at the Faculté de Pharmacie de Marseille. 1H and ^{13}C NMR chemical shifts (δ) are reported in ppm with respect to $CHCl_3$ 7.26 ppm (1H) and 77.16 ppm (^{13}C) and to $DMSO-d_6$ 2.50 ppm (1H) and 39.70 ppm (^{13}C). Elemental analyses were carried out at Spectropole, University of Aix-Marseille III.

Compounds **1**, **11** and **12** were already described.¹⁶

General Procedure for $S_{RN}1$ reaction with nitronate and malonate anions. A solution of 60% NaH (3 eq.) in DMSO under N_2 was treated with appropriate nitroalkane (3 eq.) and stirred at rt for 20 min. A solution of 6,8-dibromo-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine **1** (1 eq.) in DMSO was then

added and the mixture was irradiated with a 60 W tungsten lamp and stirred until disappearance of starting material as monitored by TLC. At this time, the mixture was poured into cold water. The aqueous solution was extracted with CH_2Cl_2 . The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column. Wanted products were recrystallized from *i*-PrOH, *s*-BuOH or cyclohexane.

Inhibitions were performed using the same protocol adding 10 mol% TEMPO or CuCl_2 with **1** simultaneously.

6,8-Dibromo-2-(2-methylprop-1-enyl)-3-nitroimidazo[1,2-*a*]pyridine (2).

Recrystallization from *i*-PrOH gave pink needles, yielding 94%. mp 149 °C. ^1H NMR (CDCl_3) δ 2.10 (d, $J = 1.0$ Hz, 3H, CH_3); 2.39 (d, $J = 1.0$ Hz, 3H, CH_3); 7.06-7.07 (m, 1H, CH); 7.92 (d, $J = 1.6$ Hz, 1H, CH); 9.58 (d, $J = 1.6$ Hz, 1H, CH). ^{13}C NMR (CDCl_3) δ 21.3 (CH_3); 28.5 (CH_3); 109.4 (C); 112.5 (CH); 114.8 (CH); 127.0 (CH); 135.6 (CH); 141.5 (C); 148.7 (C); 152.8 (C), the C- NO_2 was not observed under these experimental conditions. *Anal.* Calcd for $\text{C}_{11}\text{H}_9\text{Br}_2\text{N}_3\text{O}_2$: C, 35.23; H, 2.42; N, 11.20. Found: C, 35.47; H, 2.41; N, 11.33.

***E*-6,8-Dibromo-2-(but-1-enyl)-3-nitroimidazo[1,2-*a*]pyridine (3).**

Recrystallization from *i*-PrOH gave pink needles, yielding 83%. mp 138 °C. ^1H NMR (CDCl_3) δ 1.19 (t, $J = 7.5$ Hz, 3H, CH_3); 2.34-2.53 (m, 2H, CH_2); 7.29 (dt, $J = 15.6$ Hz, $J = 1.4$ Hz, 1H, CH); 7.48 (dt, $J = 15.6$ Hz, $J = 6.1$ Hz, 1H, CH); 7.92 (d, $J = 1.7$ Hz, 1H, CH); 9.55 (d, $J = 1.7$ Hz, 1H, CH). ^{13}C NMR (CDCl_3) δ 12.7 (CH_3); 26.5 (CH_2); 109.3 (C); 112.3 (C); 118.7 (CH); 127.0 (C); 135.9 (CH); 141.8 (C); 147.9 (CH); 148.1 (C), the C- NO_2 was not observed under these experimental conditions. *Anal.* Calcd for $\text{C}_{11}\text{H}_9\text{Br}_2\text{N}_3\text{O}_2$: C, 35.23; H, 2.42; N, 11.20. Found: C, 35.21; H, 2.40; N, 11.13.

6,8-Dibromo-2-(cyclopentylidenemethyl)-3-nitroimidazo[1,2-*a*]pyridine (4).

Recrystallization from *s*-BuOH gave brown crystals, yielding 59%. mp 156 °C. ^1H NMR (CDCl_3) δ 1.67-1.92 (m, 4H, 2x CH_2); 2.63-2.70 (m, 2H, CH_2); 3.00-3.06 (m, 2H, CH_2); 7.27-7.32 (m, 1H, CH); 7.90 (d, $J = 1.6$ Hz, 1H, CH); 9.57 (d, $J = 1.6$ Hz, 1H, CH). ^{13}C NMR (CDCl_3) δ 25.7 (CH_2); 26.9 (CH_2); 34.0 (CH_2); 37.3 (CH_2); 109.1 (C); 110.4 (CH); 112.4 (C); 127.1 (CH); 135.5 (CH); 141.7 (C); 142.4 (C); 149.2 (C); 166.6 (C). *Anal.* Calcd for $\text{C}_{13}\text{H}_{11}\text{Br}_2\text{N}_3\text{O}_2$: C, 38.93; H, 2.76; N, 10.48. Found: C, 39.03; H, 2.87; N, 10.46.

6,8-Dibromo-2-(cyclohexylidenemethyl)-3-nitroimidazo[1,2-*a*]pyridine (5).

Recrystallization from *i*-PrOH gave beige solid, yielding 91%. mp 159 °C. ^1H NMR (CDCl_3) δ 1.63-1.78 (m, 6H, 3 CH_2); 2.40-2.46 (m, 2H, CH_2); 3.03-3.09 (m, 2H, CH_2); 6.96 (s, 1H, CH); 7.92 (d, $J = 1.6$ Hz, 1H, CH); 9.58 (d, $J = 1.6$ Hz, 1H, CH). ^{13}C NMR (CDCl_3) δ 26.4 (CH_2); 27.9 (CH_2); 28.9 (CH_2); 30.9

(CH₂); 39.0 (CH₂); 109.4 (C); 112.0 (CH); 112.4 (C); 127.0 (CH); 135.5 (CH); 141.5 (C); 148.8 (C); 160.1 (C), the C-NO₂ was not observed under these experimental conditions. *Anal.* Calcd for C₁₄H₁₃Br₂N₃O₂: C, 40.51; H, 3.16; N, 10.12. Found: C, 40.01; H, 3.07; N, 9.78.

Diethyl 2-[(6,8-dibromo-3-nitroimidazo[1,2-*a*]pyridin-2-yl)methylene]malonate (6).

Recrystallization from *i*-PrOH gave yellow powder, yielding 30%. mp 179 °C. ¹H NMR (CDCl₃) δ 1.37 (t, *J* = 7.2 Hz, 3H, CH₃); 1.37 (t, *J* = 7.1 Hz, 3H, CH₃); 4.36 (q, *J* = 7.2 Hz, 2H, CH₂); 4.50 (q, *J* = 7.1 Hz, 2H, CH₂); 7.98 (d, *J* = 1.7 Hz, 1H, CH); 8.39 (s, 1H, CH); 9.54 (d, *J* = 1.7 Hz, 1H, CH). ¹³C NMR (CDCl₃) δ 14.0 (CH₃); 14.1 (CH₃); 62.1 (CH₂); 62.3 (CH₂); 111.3 (C); 113.6 (C); 126.6 (CH); 127.9 (CH); 134.9 (C); 136.3 (CH); 141.3 (C); 141.8 (C); 163.1 (C=O); 165.3 (C=O). the C-NO₂ was not observed under these experimental conditions. *Anal.* Calcd for C₁₅H₁₃Br₂N₃O₆: C, 36.69; H, 2.67; N, 8.56. Found: C, 36.86; H, 2.63; N, 8.51.

Dimethyl 2-[(6,8-dibromo-3-nitroimidazo[1,2-*a*]pyridin-2-yl)methyl]malonate (7).

Recrystallization from *i*-PrOH gave brown needles, yielding 64%. mp 172 °C. ¹H NMR (CDCl₃) δ 3.79 (s, 6H, 2xCH₃); 3.86 (d, *J* = 7.5 Hz, 2H, CH₂); 4.26 (t, *J* = 7.5 Hz, 1H, CH); 7.94 (d, *J* = 1.6 Hz, 1H, CH); 9.55 (d, *J* = 1.6 Hz, 1H, CH). ¹³C NMR (CDCl₃) δ 29.4 (CH₂); 49.1 (CH); 52.8 (2xCH₃); 110.5 (C); 112.9 (C); 126.7 (CH); 135.6 (CH); 141.1 (C); 150.3 (C); 169.0 (2xC=O), the C-NO₂ was not observed under these experimental conditions. *Anal.* Calcd for C₁₅H₁₅Br₂N₃O₆: C, 33.57; H, 2.38; N, 9.04. Found: C, 32.97; H, 2.30; N, 8.64.

Diethyl 2-[(6,8-dibromo-3-nitroimidazo[1,2-*a*]pyridin-2-yl)methyl]malonate (8).

Recrystallization from *i*-PrOH gave golden needles, yielding 57%. mp 136 °C. ¹H NMR (CDCl₃) δ 1.29 (t, *J* = 7.2 Hz, 6H, 2xCH₃); 3.84 (d, *J* = 7.6 Hz, 2H, CH₂); 4.23 (q, *J* = 7.2 Hz, 4H, 2xCH₂); 4.24 (t, *J* = 7.6 Hz, 1H, CH); 7.93 (d, *J* = 1.6 Hz, 1H, CH); 9.54 (d, *J* = 1.6 Hz, 1H, CH). ¹³C NMR (CDCl₃) δ 14.1 (2xCH₃); 29.3 (CH₂); 49.4 (CH); 61.7 (2xCH₂); 110.4 (C); 112.8 (C); 126.7 (CH); 135.6 (CH); 141.1 (C); 150.6 (C); 168.6 (2xC=O), the C-NO₂ was not observed under these experimental conditions. *Anal.* Calcd for C₁₅H₁₅Br₂N₃O₆: C, 36.54; H, 3.07; N, 8.52. Found: C, 36.73; H, 3.12; N, 8.78.

Diethyl 2-[(6,8-dibromo-3-nitroimidazo[1,2-*a*]pyridin-2-yl)methyl]-2-methylmalonate (9).

Recrystallization from cyclohexane gave brown powder, yielding 61%. mp 122 °C. ¹H NMR (CDCl₃) δ 1.28 (t, *J* = 7.2 Hz, 6H, 2xCH₃); 1.53 (s, 3H, CH₃); 3.90 (s, 2H, CH₂); 4.25 (q, *J* = 7.2 Hz, 4H, 2xCH₂); 7.92 (d, *J* = 1.7 Hz, 1H, CH); 9.52 (d, *J* = 1.7 Hz, 1H, CH). ¹³C NMR (CDCl₃) δ 14.0 (2xCH₃); 20.1 (CH₃); 35.0 (CH₂); 53.6 (2xCH₂); 61.7 (C); 110.3 (C); 112.9 (C); 126.8 (CH); 131.3 (C); 135.5 (CH); 140.9 (C); 149.5 (C); 171.3 (2xC=O). *Anal.* Calcd for C₁₆H₁₇Br₂N₃O₆: C, 37.89; H, 3.38; N, 8.29. Found: C, 37.89; H, 3.38; N, 8.25.

Diethyl 2-[(6,8-dibromo-3-nitroimidazo[1,2-*a*]pyridin-2-yl)methyl]-2-phenylmalonate (10).

Recrystallization from *i*-PrOH gave yellow needles, yielding 67%. mp 149 °C. ¹H NMR (DMSO-*d*₆) δ 1.17 (t, *J* = 7.0 Hz, 6H, 2xCH₃); 4.12 (s, 2H, CH₂); 4.16-4.34 (m, 4H, 2xCH₂); 7.24-7.31 (m, 5H, 5xCH); 8.42 (d, *J* = 1.6 Hz, 1H, CH); 9.35 (d, *J* = 1.6 Hz, 1H, CH). ¹³C NMR (DMSO-*d*₆) δ 14.2 (2xCH₃); 36.4 (CH₂); 61.8 (C); 62.0 (2xCH₂); 110.3 (C); 112.2 (C); 127.7 (CH); 128.0 (CH); 128.1 (2xCH); 128.5 (2xCH); 131.5 (C); 136.2 (CH); 137.2 (C); 140.8 (C); 149.0 (C); 169.5 (2xC=O). *Anal.* Calcd for C₂₁H₁₉Br₂N₃O₆: C, 44.31; H, 3.36; N, 7.38. Found: C, 44.39; H, 3.39; N, 7.41.

6,8-Dibromo-2-[(4-chlorophenylsulfonyl)methyl]-3-nitroimidazo[1,2-*a*]pyridine (13).

To a solution of sodium 4-chlorophenylsulfinate (300 mg, 1.51 mmol) in DMSO under N₂, was added **1** (300 mg, 0.812 mmol). The solution was stirred at rt for 2 h. After disappearance of **1** (as monitored by TLC), the mixture was poured into 200 mL of cold water. Precipitated solid was filtered and air dried to give after recrystallization from *s*-BuOH, 310 mg (75 %) of **11** as shiny pale yellow plates. mp 194 °C. ¹H NMR (DMSO-*d*₆) δ 5.29 (s, 2H, CH₂); 7.65 (d, *J* = 8.7 Hz, 2H, 2xCH); 7.78 (d, *J* = 8.7 Hz, 2H, 2xCH); 8.45 (d, *J* = 1.5 Hz, 1H, CH); 9.38 (d, *J* = 1.5 Hz, 1H, CH). ¹³C NMR (DMSO-*d*₆) δ 55.9 (CH₂); 79.3 (C); 110.7 (C); 112.4 (C); 127.5 (CH); 129.5 (2xCH); 130.6 (2xCH); 131.7 (C); 136.3 (CH); 137.5 (C); 139.5 (C); 141.0 (C). HRMS *m/z* Calcd for C₁₄H₉Br₂ClN₃O₄S: 509.8342. Found: 509.8346.

2-[(6,8-Dibromo-3-nitroimidazo[1,2-*a*]pyridine-2-yl)methylsulfanyl]benzo[*d*]thiazole (14).

To a solution of 60% NaH (32 mg, 0.812 mmol, 1.2 eq.) in DMSO under N₂, was added 2-sulfanylbenzothiazole (136 mg, 0.812 mmol, 1.2 eq.). The solution was stirred for 20 min at rt and added **1** (250 mg, 0.678 mmol, 1 eq.) and additional stirring was allowed for 20 min. At this time, starting material had disappeared as monitored by TLC (eluted with CHCl₃/petroleum ether, 7/3). The solution was then poured into 200 mL of cold water and the precipitated solid was filtered and air dried to give, after recrystallization from *s*-BuOH, 305 mg (90%) of **14** as beige crystals. mp 254 °C. ¹H NMR (DMF-*d*₇) δ 5.27 (s, 2H, CH₂); 7.36-7.55 (m, 2H, 2xCH); 7.86-7.90 (m, 1H, CH); 8.03-8.07 (m, 1H, CH); 8.43 (m, 1H, CH); 9.53 (d, *J* = 1.6 Hz, 1H, CH). *Anal.* Calcd for C₁₅H₈Br₂N₄O₂S₂: C, 36.02; H, 1.61; N, 11.20; S, 12.82. Found: C, 35.24; H, 1.60; N, 11.87; S, 12.25. HRMS *m/z* Calcd for C₁₅H₈Br₂N₄O₂S₂: 500.8508. Found: 500.8513.

6-Bromo-3-nitro-8-phenylsulfanyl-2-phenylsulfanylmethylimidazo[1,2-*a*]pyridine (15).

To a solution of 60% sodium hydride (71 mg, 1.786 mmol, 2.2 eq.) in DMSO under N₂, was added thiophenol (0.18 mL, 1.786 mmol, 2.2 eq.). The solution was stirred for 10 min and added **1** (300 mg, 0.812 mmol, 1 eq.) and additional stirring was allowed for 25 min. At this time, starting material had disappeared as monitored by TLC (eluted with CHCl₃/petroleum ether, 7/3). The solution was then poured into 200 mL of cold water and extracted with EtOAc (3 x 30 mL). Combined organic layers were

washed with brine (5 x 20 mL), dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The oily residue was precipitated from petroleum ether and recrystallization from *i*-PrOH gave 272 mg of **15** (71% yield) as yellow crystals. mp 171 °C. ¹H NMR (CDCl₃) δ 4.67 (s, 2H, CH₂); 6.82 (d, *J* = 1.7 Hz, 1H, CH); 7.17-7.33 (m, 3H, 3xCH); 7.47-7.66 (m, 7H, 7xCH); 9.26 (d, *J* = 1.7 Hz, 1H, CH). ¹³C NMR (CDCl₃) δ 33.2 (CH₂); 111.7 (C); 123.6 (CH); 126.9 (CH); 127.7 (C); 127.9 (CH); 128.9 (2xCH); 130.4 (2xCH); 130.5 (CH); 130.6 (2xCH); 133.2 (C); 135.1 (C); 135.7 (2xCH); 139.9 (C); 149.2 (C), the C-NO₂ was not observed under these conditions. *Anal.* Calcd for C₂₀H₁₄BrN₃O₂S₂: C, 50.85; H, 2.99; N, 8.90; S, 13.58. Found: C, 50.87; H, 3.01; N, 8.92; S, 13.85.

Same conditions with additional 10 mol% CuCl₂ provided **16** (described below) yielding 67%.

6,8-Dibromo-3-nitro-2-phenylsulfanylmethylimidazo[1,2-*a*]pyridine (16).

Under a nitrogen atmosphere, a solution of tetrabutylammonium hydroxide (40% in water) was treated with thiophenol (0.649 mmol) for 20 min. A solution of **1** (0.541 mmol) in toluene was then added and the mixture was irradiated with a 60 W tungsten lamp and stirred at rt for 4 h. At this time, the mixture was poured into cold water (150 mL). The aqueous solution was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with water (6 x 15 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column. Recrystallization from *i*-PrOH gave 151 mg of **16**, yielding 63%. mp 140 °C. ¹H NMR (CDCl₃) δ 4.66 (s, 2H, CH₂); 7.21-7.32 (m, 3H, 3xCH); 7.43-7.50 (m, 2H, 2xCH); 7.96 (d, *J* = 1.6 Hz, 1H, CH); 9.54 (d, *J* = 1.6 Hz, 1H, CH). ¹³C NMR (CDCl₃) δ 33.3 (CH₂); 110.7 (C); 113.0 (C); 126.8 (CH); 127.2 (CH); 128.9 (2xCH); 130.9 (2xCH); 134.7 (C); 135.8 (CH); 141.0 (C); 150.2 (C), the C-NO₂ was not observed under these conditions. *Anal.* Calcd for C₁₄H₉Br₂N₃O₂S: C, 37.95; H, 2.05; N, 9.48; S, 7.24. Found: C, 37.99; H, 2.06; N, 9.45; S, 7.19.

X-Ray structure determination

Data were measured on a Bruker-Nonius KappaCCD diffractometer with a graphite-monochromated Mo-Kα radiation at 293 (2) K.

Crystal data of 15: Dark yellow prism, C₂₀H₁₄BrN₃O₂S₂, crystal dimensions 0.2 x 0.15 x 0.15 mm. *M*=472.37, orthorhombic, space group P 21 21 21, *a*=8.5520(1), *b*=13.4949(2), *c*=17.4150(4) Å, α=90.00°, β=90.00°, γ=90.00°, *V*=2009.84(6) Å³, *Z*=4, μ = 2.274 mm⁻¹, *F*(000) = 952, index ranges 0 ≤ *h* ≤ 11, 0 ≤ *k* ≤ 18, -23 ≤ *l* ≤ 23. 253 variables and 0 restraints, were refined for 3405 reflections collected with *I* ≥ 2σ₁ to *R* = 0.0392, w*R*² = 0.0963, GoF = 1.006.

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