

Convenient Synthesis of Methyl 1-Methyl-2,4-dibromo-5-imidazolecarboxylate

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Three syntheses of methyl 1-methyl-2,4-dibromo-5-imidazolecarboxylate (**8**) are presented. One proceeds from sarcosine via ring closure, bromination, and desulfurization. The second uses *N*-methylimidazole, polybromination, and selective halogen-metal interchange. The third and most efficient and preparatively useful route begins with diamino-maleonitrile (**13**). Ring closure with triethyl orthoformate followed by methylation and hydrolysis affords 1-methyl-4,5-imidazolidicarboxylic acid (**16**). Regioselective decarboxylation followed by esterification yields methyl 1-methyl-5-imidazolecarboxylate (**18**). Subsequent dibromination gives the completely substituted imidazole **8**. The primary purification in this sequence is fractional sublimation of **18** after the esterification step. An overall yield of 26% is achieved from diamino-maleonitrile (**13**) to methyl 1-methyl-2,4-dibromo-5-imidazolecarboxylate (**8**), which is a key intermediate for the synthesis of tricyclic imidazo-cooked food mutagens.

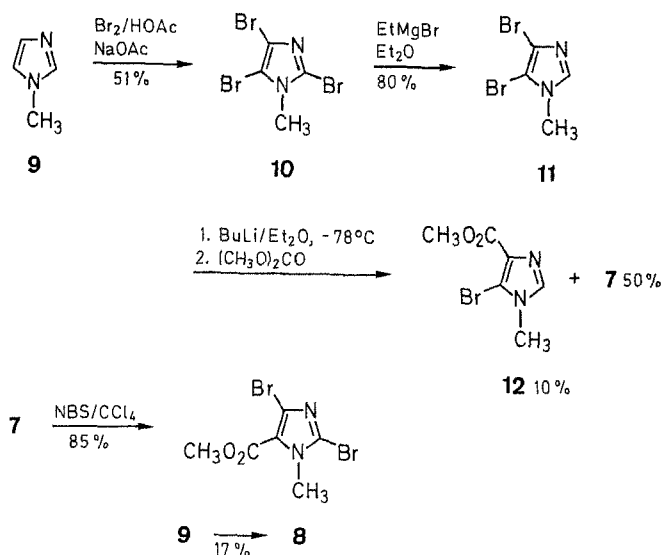
In the development of an isomerically unambiguous synthesis of a number of imidazoquinoline mutagens isolated from fried beef and fish,¹⁻⁴ the fully functionalized imidazole methyl 1-methyl-2,4-dibromo-5-imidazolecarboxylate (**8**) was needed. A regioselective efficient synthesis of **8** was required that could readily be carried out on a moderate scale. We now report the experimental evaluation of three routes to this dibromoimidazole ester **8**.

The first sequence examined employed the regio controlled synthesis of *N*-methyl substituted imidazoles originally reported by Jones.⁵ As shown in Scheme A, sarcosine (**1**) was first converted to its methyl ester hydrochloride **2**, then *N*-formylation followed by Claisen condensation with methyl formate and subsequent cyclization with potassium thiocyanate afforded methyl 1-methyl-2-mercapto-5-imidazolecarboxylate (**4**). Alkylation of **4** with methyl iodide in the presence of potassium carbonate in dry methanol resulted in a 95% yield of the 2-methylthio imidazole **5**. Bromination with *N*-bromosuccinimide (NBS) in the presence of 2,2'-azobisisobutyronitrile (AIBN) as catalyst in carbon tetrachloride afforded monobromo imidazole **6** in 46% yield. Selective desulfurization with W-2

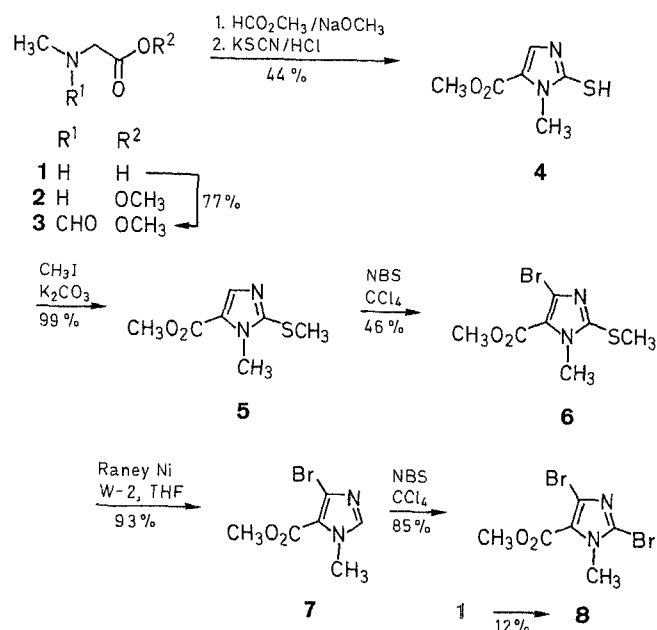
Raney Nickel could be effected without debromination and gave the 4-bromoimidazole ester **7**. Now, bromination of the remaining open 2-position was easily achieved in 85% yield with NBS to give the dibromoimidazole ester **8**.

Despite an overall yield of only 12%, this sequence does offer easy purifications and is suitable for large scale preparation of **8** in seven steps. More importantly, it allows for the unambiguous introduction of bromine at C-4 and the preparation of such a monobromo imidazole unsubstituted at C-2, unattainable by normal bromination methods.⁶

Our second route to dibromoimidazole ester **8** was based on recent work involving the synthesis of *N*-protected 4,5-disubstituted imidazoles via successive halogen-metal exchange reactions as shown in Scheme B.^{7,8}



Scheme B



Scheme A

1-Methyl-2,4,5-tribromoimidazole (**10**) was prepared by total bromination⁹ from 1-methylimidazole (**9**) in 51% yield. Treatment of tribromoimidazole **10** with 100 mol% of ethylmagnesium bromide in dry tetrahydrofuran at room temperature followed by a water quench afforded a 1/1 mixture of 1-methyl-2,4-dibromo- and 1-methyl-4,5-dibromoimidazole (**11**) as analyzed by $^1\text{H-NMR}$. However, when the reaction was performed in dry ether at room temperature only the more reactive 2-halogen was exchanged. A single product was obtained in 80% yield corresponding to **11** by comparison with an authentic sample.^{6,10} This difference in product distribution between tetrahydrofuran and ether had not been observed previously.⁷ Subsequent treatment of **11** with *n*-butyllithium in ether followed by dimethyl carbonate at -78°C afforded a mixture of the two possible esters **7** and **12**. Chromatographic separation led to the pure major product, the 4-bromo regioisomer **7**, and the minor product, methyl 1-methyl-5-bromo-4-imidazolecarboxylate (**12**). In each case, the structure was established by hydrogenolytic debromination and comparison with authentic samples of the resulting 1,4 and 1,5 esters.¹¹ Subsequent bromination of **7** eventually yielded the target dibromo ester **8**.

This four-step procedure from *N*-methylimidazole yielded **8** in an overall yield of 17%. Thus, this sequence does provide an acceptable preparation of **8**; however, a significant drawback was the chromatographic separation required following the second halogen-metal exchange. Even though separation was not extremely difficult, it was tedious for the quantities of **8** required.

The third and preferred process for the preparation of dibromo ester **8** is outlined in Scheme C. Condensation of diamino-maleonitrile (**13**) and triethyl orthoformate in anisole affords 4,5-dicyanoimidazole (**14**) in 83% yield.¹² Methylation with dimethyl sulfate then gives 1-methyl-4,5-dicyanoimidazole (**15**) in 85% yields.¹³ Treatment of **15** with refluxing 6*N* sodium hydroxide for 2 h followed by acidification to pH 2 with 3*N* hydrochloric acid gives 1-methyl-4,5-imidazoledicarboxylic acid (**16**) in 81% yield. Alternatively, this sequence to diacid **16** may be done with the initial reaction performed in diglyme rather than anisole. Increased solubility in diglyme allows for

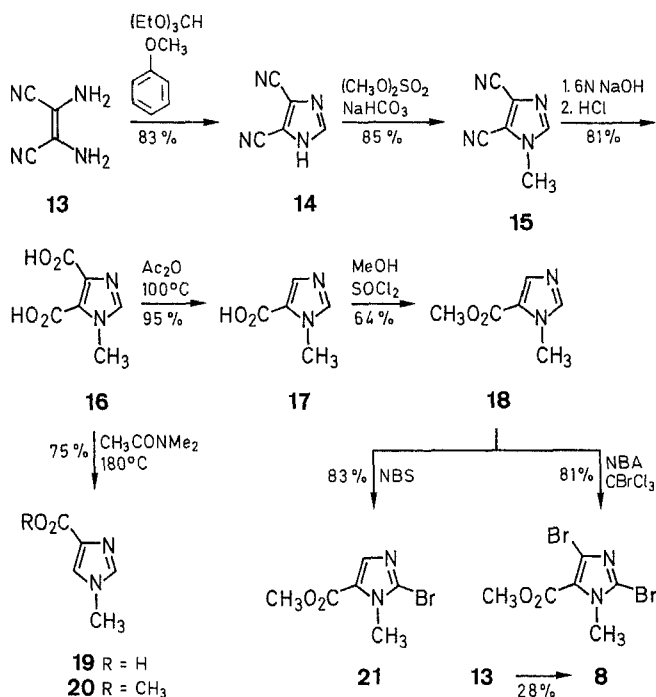
much easier large scale preparation of **16** in comparable overall yield. However, the intermediate **14** is not readily isolated in pure form by this alternate route.

It has been reported¹⁴ that diacid **16** can be selectively decarboxylated at the 5-position to give 1-methyl-4-imidazolecarboxylic acid (**19**) by treatment in *N,N*-dimethylacetamide at 180°C for 4 h, whereas heating in acetic anhydride at 100°C for 4 h leads to exclusive decarboxylation at the 4-position giving excellent yields of 1-methyl-5-imidazolecarboxylic acid (**17**).

We have found that treatment of diacid **16** under either of the reported conditions affords imidazole monocarboxylic acid mixtures. Without purification, the acid mixtures were esterified for purification and analytical purposes. Chromatography (HPLC and GC) revealed that the acetic anhydride decarboxylation is quite selective giving, after esterification, a mixture of 5-ester **18** (94%), 4-ester **20**, (3%), and the corresponding diester (3%). On the other hand, the thermal decarboxylation in *N,N*-dimethylacetamide is not as selective giving a mixture consisting of 78% of **20**, 18% of **18**, and 3% of the diester. The HPLC analysis detection level for the 4-ester in the presence of the 5-ester is approximately 0.5%, while the sensitivity of the GC analysis is 0.2%, and the latter also has the advantage of being more rapid. Furthermore, in accordance with previously published NMR data,¹⁵ the 4-ester **20** and 5-ester **18** can be distinguished by their cross ring coupling constants, which are, *J* = 1.30 and 0.93 Hz, respectively.

The major purification for the sequence of Scheme C is performed easily and effectively at this methyl ester stage by fractional sublimation. The 5-ester **18** is more volatile than the 4-ester **20** and may be purified by fractional sublimation *in vacuo* at room temperature yielding a colorless crystalline solid. The 4-ester **20** may also be sublimed *in vacuo* at a higher temperature, e.g. 60°C. Thus purification of these esters by fractional sublimation is quite simple and amenable to large scale preparations. In addition, it fulfills the regiochemical purity specifications for the synthesis of dibromo ester **8**.

The last conversion of this route was to dibrominate ester **18** to give **8**. Treatment of **18** with bromine in refluxing chloroform gave only decomposed products while NBS in refluxing carbon tetrachloride with AIBN gave the 2-monobrominated product **21** in a clean 83% yield. It was obvious from these results that this halogenation proceeded by a radical chain mechanism rather than by a simple electrophilic bromination. Thus, when **18**



Scheme C

Table. ¹H-NMR Data for *N*-Methyl Imidazoles (CDCl₃, δ)

Product	Substituent at Position			N-CH ₃	Assignment for Substituent at Position		
	C-2	C-4	C-5		C-2	C-4	C-5
4	SCH ₃	H	CO ₂ CH ₃	3.80	2.67	7.71	3.83
6	SCH ₃	Br	CO ₂ CH ₃	3.78	2.67	—	3.88
7	H	Br	CO ₂ CH ₃	3.90	7.47	—	3.91
8	Br	Br	CO ₂ CH ₃	3.91	—	—	3.91
11	H	Br	Br	3.62	7.48	—	—
12	H	CO ₂ CH ₃	Br	3.89	7.50	—	3.90
15	H	CN	CN	3.92	7.70	—	—
16	H	CO ₂ H	CO ₂ H	3.91	7.79	—	—
17	H	H	CO ₂ H	3.92	7.62	8.51	—
18^a	H	H	CO ₂ CH ₃	3.81	7.50	7.68	3.87
20^b	H	CO ₂ CH ₃	H	3.73	7.44	3.87	7.57
21	Br	H	CO ₂ CH ₃	3.85	—	7.67	3.91

^a Doublet, *J*_{2,4} = 0.93 Hz.

^b Doublet, *J*_{2,5} = 1.30 Hz.

was treated with *N*-bromoacetamide (NBA) and AIBN in bromotrichloromethane or a bromotrichloromethane/carbon tetrachloride mixture at 50°C for 60 hours, a slow and what appeared to be clean conversion of **18** ensued to the 2-mono-bromo product **21**, followed by conversion to the dibromo ester **8**. Two advantages seemed apparent in using these reaction conditions: (i) the use of bromotrichloromethane¹⁶⁻¹⁸ provided an additional bromine radical carrier thus promoting the chain reaction; and (ii) the milder reaction conditions reduced the possibility of molecular bromine formation via a radical termination step. It was later found that the use of AIBN as a radical initiator was unnecessary since identical results were obtained in its absence. Apparently, ambient light and 50°C were sufficient initiators to induce radical bromination.

The yields were affected by two variables: reaction time and the amount of silica used in the purification. Mass recoveries varied depending on reaction time; optimum yields were obtained at 36 h. To accurately assess the presence of monobromo ester **21** in a batch of **8**, GC/MS analysis was used. It was established that careful column chromatography affords dibromo ester **8** free of any monobromo ester. However, two other impurities were discovered during this analysis and confirmed by high resolution mass spectrometry; to a slight extent the imidazole ring had been chlorinated as well as brominated.

Considering that such a halogenation is free radical in nature, it is not surprising that some chlorination did occur. The two impurities together represented 14% of the sample and corresponded to the two monochloro monobromo esters. Changing to pure bromoform as the solvent system afforded dibromo ester **8** > 99% free from chlorobromo impurities. The grade of bromoform used appears to be of importance in this reaction since the presence of chlorodibromomethane in one sample of bromoform led to a 4% chlorobromo impurity in the final product. Since free radical brominations are commonly conducted in chlorinated solvents, our experience of detecting some chlorinated products should serve as a caveat.

As noted previously, the selective decarboxylation sequence of Scheme C became the preferred sequence for the preparation of dibromo ester **8**. Not only because this sequence offered an overall yield of 28% from **13** using anisole or 31% using diglyme, but, more importantly, because it provides an unambiguous synthesis, with simple purifications, of the key regio isomer **18**. In addition, this sequence also allows for the selective preparation of the 1,4-regioisomer derivatives. A summary of ¹H-NMR data for all the compounds discussed is presented in the Table.

THF was distilled from sodium and benzophenone. MeOH was distilled from Mg(OMe)₂. IR spectra were obtained with a Perkin-Elmer 1320 Infrared spectrophotometer. ¹H- and ¹³C-NMR spectra were determined using UCB spectrometers (superconducting, FT instruments) or a Bruker AM-500 spectrometer at the indicated frequencies using internal TMS (CDCl₃) or Me₃SiCD₂CD₂CO₂Na, (TSP) (water) as internal reference. GC was performed on a Hewlett-Packard Model 5890 gas chromatograph equipped with a model 5970 selective mass detector and 30 meter Durabond DB-1 or DB-5 columns with 0.25 mm inside diameter and film thickness of 0.25 μ.

HPLC was performed on an Altex system composed of two model 110A pumps, a model 210 injector, a model 420 system controller and a Hitachi model 100-30 UV-VIS spectrophotometer equipped with an Altex analytical flow cell. A 4.5 × 250 cm column packed with a 10 μ Altex Ultra Pack ODS was used with a 4.5 × 50 mm pre-column packed with Whatman Co-Pell ODS and a 4.5 × 250 mm solvent presaturating column packed with 5 μ Microsorb silica. A 50/50 MeCN/H₂O solvent mixture at 1.3 mL/min flow rate was used with detection at 254 nm. Elemental analyses were performed by the Micro Analytical Laboratory,

College of Chemistry, University of California, Berkeley. Column chromatography was performed with 70-30 (gravity) or 230-400 (5 psi, low pressure liquid chromatograph, LPLC) mesh silica gel (Merck). All melting points were determined with a Büchi melting point apparatus and are uncorrected.

Sarcosine Methyl Ester Hydrochloride (2):

To an ice-cold solution of sarcosine (**1**; 35.6 g, 0.4 mol) in dry MeOH (500 mL) is added dropwise SOCl₂ (120 mL), and the solution is refluxed for 3 h. Solvent is evaporated in vacuum and traces of SOCl₂ removed by adding benzene and repeating the evaporation. The residue is washed with dry ether and dried in a desiccator to afford **2**; yield: 48 g (90%); mp 173-175°C (dec) (Lit.⁵ mp 175°C, dec).

¹H-NMR (D₂O): δ = 2.83 (s, 3H); 3.9 (s, 3H); 4.08 (s, 2H).

N-Formylsarcosine Methyl Ester (3):

To a solution of **2** (33.5 g, 0.244 mol) in hot HCO₂H (25 mL) is added a solution of HCO₂Na (25 g) in hot HCO₂H (40 mL) in one portion. After standing at ambient temperature for 2 h, the solution is filtered, and the filtrate is treated with Ac₂O (5 × 15 mL) while the temperature is raised to 60°C. The cloudy mixture is then diluted with acetone (100 mL), filtered and concentrated. The residue is distilled using a Kugelrohr apparatus to give **3** as a clear oil; yield: 26.6 g (85%); bp 100°C (bath temp)/5 mbar (Lit.⁵ bp 97-100°C/5 mbar).

Methyl 1-Methyl-2-mercapto-5-imidazolecarboxylate (4):

To **3** (5 g, 0.038 mol) and HCO₂Me (6.86 g, 0.144 mol) at 0°C is added a suspension of NaOMe (2.26 g, 0.04 mol) in dry benzene (10 mL) over a period of 1 h with stirring. The solution is allowed to come to ambient temperature and stirred for another 1.5 h. Water (25 mL) is added and stirred until all solid has dissolved. The benzene is decanted and conc. HCl (7.0 mL, 45.7 mmol) is added at 0°C. KSCN (4.37 g, 45 mmol) is then added in four portions, the mixture is warmed on a steam bath for 3 h, then left at ambient temperature overnight. The white crystals formed are collected by filtration, washed with water and air-dried to afford **4**; yield: 2.9 g (44%); mp 189-191°C (dec) (Lit.⁵ mp 190-191°C, dec).

Methyl 1-Methyl-2-methylthio-5-imidazolecarboxylate (5):

To a suspension of **4** (10.0 g, 0.582 mol), and calcined K₂CO₃ (5.0 g), in dry MeOH (75 mL) is added MeI (4.31 mL, 0.7 mol) with stirring at ambient temperature. After 2 min, the mixture is filtered and the filtrate concentrated to afford **5** as a white solid; yield: 10.7 g (99%); mp 43-45°C.

C ₇ H ₁₀ N ₂ O ₂ S	calc.	C 45.15	H 5.41
(186.2)	found	45.20	5.25

¹H-NMR (CDCl₃): δ = 2.67 (s, 3H); 3.83 (s, 6H); 7.71 (s, 1H).

Methyl 4-Bromo-1-methyl-2-methylthio-5-imidazolecarboxylate (6):

To a solution of **5** (2.0 g, 10.7 mmol) in CHCl₃ (60 mL, dried over MgSO₄ prior to use) and CCl₄ (60 mL, dried over activity I alumina prior to use) is added NBS (2.1 g, 22.5 mmol) and AIBN (90 mg, 0.54 mmol). The mixture is further heated at 65°C with stirring for 15 h, then it is evaporated and the residue chromatographed (LPLC, CHCl₃) to yield **6** as a crude solid. Recrystallization from isooctane affords pure **6**; yield: 1.1 g (46%); mp 96-97.5°C.

C ₇ H ₉ BrN ₂ O ₂ S	calc.	C 31.70	H 3.42	N 10.56
(265.2)	found	32.10	3.22	10.69

¹H-NMR (500 MHz, CDCl₃): δ = 2.67 (s, 3H); 3.78 (s, 3H); 3.88 (s, 3H).

1-Methyl-2,4,5-tribromoimidazole (10):

To a mixture of 1-methylimidazole (**9**; 24.6 g, 0.30 mol) and NaOAc (102.0 g, 1.2 mol) in glacial AcOH (500 mL) is added dropwise a solution of Br₂ (146.0 g, 0.9 mol) in glacial AcOH (50 mL) dropwise with vigorous stirring, and cooling to maintain the temperature below 60°C. After the final addition, the mixture is stirred at ambient temperature for 2 h, then poured onto ice (1 L), stirred and filtered. Crystallization from AcOH/water (85:15) affords **10**; yield: 48.7 g (51%); mp 88-89°C (Lit.⁹ mp 93-94°C).

IR (CCl₄): ν = 2960, 1500, 1458, 1413, 1366, 1316, 1221, 1134, 1090, 975 cm⁻¹.

¹H-NMR (180 MHz, CDCl₃): δ = 3.64 (s).

1-Methyl-4,5-dibromoimidazole (11):

To a solution of **10** (15.9 g, 0.05 mol) in dry ether (500 mL) is added EtMgBr (42 mL, 0.05 mol, 1.2 M in ether) slowly at ambient tempera-

ture. After 3 h, the solvent is evaporated, cold water (400 mL) is added, the ether phase is separated, and the aqueous layer is extracted with CH_2Cl_2 (3 \times 150 mL). The organic layers are combined, dried (Na_2SO_4) and evaporated to give **11**; yield: 9.5 g (80%); mp 78–79°C (hexane) (Lit.¹⁰ mp 79–80°C).

¹H-NMR (180 MHz, CDCl_3): δ = 3.64 (s, 3H); 7.49 (s, 1H).

Methyl 1-Methyl-4-bromo-5-imidazolecarboxylate (7):

Method A: To a solution of **6** (30 mg, 0.0113 mmol) in THF (5 mL) at 0°C is added wet W-2 Raney nickel (10 mg). The mixture is warmed to ambient temperature and after 30 min the solution is decanted and evaporated to afford **7**; yield: 24 mg (93%).

Method B: To a solution of **11** (0.24 g, 1 mmol) in dry ether (10 mL) is added dropwise a 1.53 M hexane solution of BuLi (0.65 mL, 1 mmol) at –78°C with stirring. Dimethyl carbonate (0.10 g, 0.08 mL, 1.1 mmol) is then added, the mixture is allowed to warm to room temperature, concentrated and diluted with CH_2Cl_2 (25 mL). The organic phase is washed with water (25 mL), brine (10 mL), dried (Na_2SO_4), and evaporated to give a light-yellow oil (0.21 g). Purification by LPLC (EtOAc /Hexane, 1:1) affords **7**; yield: 0.1 g (50%); mp 91–94°C.

$\text{C}_6\text{H}_7\text{BrN}_2\text{O}_2$ calc. C 32.90 H 3.22 N 12.79
(219.1) found 32.65 3.18 12.78

¹H-NMR (180 MHz, CDCl_3): δ = 3.90 (s, 3H); 3.91 (s, 3H); 7.47 (s, 1H).

Continued chromatography gives **12** as pale yellow crystals; yield: 0.02 g (10%); mp 150–154°C.

¹H-NMR (180 MHz, CDCl_3): δ = 3.89 (s, 3H); 3.90 (s, 3H); 7.5 (s, 1H).

4,5-Dicyanoimidazole (14):

A mixture of diaminomaleonitrile (**13**; 108.1 g, 1 mol) and triethyl orthoformate (178.0 g, 1.2 mol) in anisole (1200 mL) is heated in a bath at 135°C, while EtOH (70 g) is distilled out over a 2 h period. NaOMe (4 g, 75 mmol) is added and heating continued until no more distillate is collected. The solution is filtered hot, and the filtrate cooled to afford **14**; yield: 98.0 g (83%); mp 172–173°C (water) (Lit.¹² mp 175°C).

1-Methyl-4,5-dicyanoimidazole (15):

To a suspension of **14** (45.7 g, 0.38 mol) in water (600 mL) is added in portions, a solution of NaHCO_3 (55.6 g, 0.66 mol) in water (100 mL). The mixture is heated to a bath temperature of 65°C, and dimethyl sulfate (73.25 g, 0.58 mol) is added dropwise over 60 min. After stirring at 65°C for 1 h, the mixture is allowed to cool, then extracted with EtOAc (4 \times 400 mL). The combined organic layer is washed with 0.5 M aq. NaHCO_3 solution (3 \times 300 mL), dried (Na_2SO_4), and evaporated to afford **15**; yield: 43.5 g (85%); mp 87–89°C (Lit.¹³ mp 89.0–89.5°C).

¹H-NMR (250 MHz, CDCl_3): δ = 3.90 (s, 3H); 7.69 (s, 1H).

1-Methyl-4,5-imidazoledicarboxylic Acid (16):

Method A: A solution of **15** (105.0 g, 0.796 mol) in 6 N NaOH (750 mL) is refluxed for 2 h with vigorous stirring. The hot solution is carefully acidified to pH 2 with conc. HCl. Cooling to ambient temperature, filtration, and drying at 100°C overnight gives **16**; yield: 108.8 g (81%); mp 259–260°C (Lit.¹³ mp 253.5–254°C).

¹H-NMR (250 MHz, D_2O): δ = 3.90 (s, 3H); 7.78 (s, 1H).

Method B; from **13** using diglyme: To diglyme (100 mL) is added diaminomaleonitrile (**13**; 30 g, 0.27 mol) and triethyl orthoformate (54 mL, 0.32 mol). The homogeneous mixture is heated to a bath temperature of 135°C with stirring until distillation of EtOH ceases. NaOMe (1.0 g, 20 mmol), is added slowly and heating continued until no more distillate is collected. The diglyme is then removed by distillation in vacuum (135°C/21 mbar), removing the final traces of diglyme at 0.13 mbar. To the residue is added water (250 mL), followed by careful addition of NaHCO_3 (42 g, 0.5 mol). The solution is heated to 65°C with stirring, dimethyl sulfate (38 mL, 0.41 mmol) is added dropwise over 1 h and the solution is stirred at 65°C for 1 h. Cooling is followed by extraction with 5% MeOH/EtOAc (4 \times 250 mL). The combined organic layer is washed with brine, dried (Na_2SO_4), and evaporated, and the residue of crude **15** is refluxed for 2 h with stirring in 6 N NaOH (300 mL). Acidification to pH 2 with conc. HCl gives a light brown solid that is purified by suspending it in water (250 mL), then adding solid NaHCO_3 until the solid dissolves. The solution is then carefully acidified with 4 N HCl and allowed to crystallize at 0°C to give **16**; yield: 25.5 g (54% from **13**) mp 254–256°C (Lit.¹³ mp 253.5–254°C).

1-Methyl-5-imidazolecarboxylic Acid (17):

A mixture of **16** (21.0 g, 0.12 mol) and Ac_2O (600 mL, dried over 4 Å sieves) is heated at a bath temperature of 100°C for 4 h with vigorous stirring. The mixture is evaporated in vacuum, and the residue is triturated with acetone and azeotropically dried with toluene to afford **17**; yield: 14.6 g (95%); mp 245–248°C (dec) (Lit.¹³ mp 256–257°C, dec).

¹H-NMR (250 MHz, D_2O): δ = 3.92 (s, 3H); 7.62 (d, 1H, J = 0.93 Hz); 8.51 (d, 1H, J = 0.93 Hz).

Methyl 1-Methyl-5-imidazolecarboxylate (18):

To MeOH (250 mL) cooled to –45°C (MeCN/ CO_2 bath) is added SOCl_2 (36.5 mL). After 30 min, a suspension of crude acid **17** (20.1 g, 0.16 mol) in MeOH (250 mL) is added in several portions and the mixture is refluxed for 24 h. Upon cooling to 40°C, solid NaHCO_3 is added to raise the pH to 8, the mixture is filtered, and the filtrate evaporated in the presence of silica (230–400 mesh) to pre-adsorb the mixture onto silica which is washed with CHCl_3 (3 \times 35 mL) through a 2 inch silica plug in a filtration funnel. The CHCl_3 is evaporated, and the residue is sublimed (25°C, 0.013 mbar) to give **18**; yield: 14.2 g (64%); mp 56–57°C (Lit.¹⁰ mp 56–57°C); HPLC, R_t = 10.8 min.

GC/MS (oven temp. = 110°C for 5 min, ramp = 20°C/min, column type = DB-5, gas flow rate 2.0 mL/min, R_t = 4 min): m/z (%) = 140 (M^+ , 63); 109 (100).

IR (CCl_4): ν = 3700, 3400, 3020, 2970, 2870, 1720, 1535 cm^{-1} .

¹H-NMR (500 MHz, CDCl_3): δ = 3.81 (s, 3H); 3.87 (s, 3H); 7.5 (d, 1H, J = 0.93 Hz); 7.68 (d, 1H, J = 0.93 Hz).

¹³C-NMR (125 MHz, CDCl_3): δ = 33.92, 51.34, 122.89, 137.52, 142.36, 160.72.

If the residue is an oil prior to sublimation, the diester contamination may be removed by first distilling out the monoester (60°C/0.013 mbar) in a Kugelrohr apparatus.

Methyl 2-Bromo-1-methyl-5-imidazolecarboxylate (21):

To a solution of **18** (400 mg, 2.8 mmol) in CCl_4 (50 mL) is added NBS (1.0 g, 5.8 mmol) and AIBN (23 mg, 0.14 mmol). The mixture is warmed to 60°C for 50 h with stirring, then filtered and evaporated, affording yellow-crystals of crude **21**; yield: 0.51 g (83%). Purification by sublimation (45°C/0.013 mbar) affords pure **21**; mp 65–67°C; GC/MS (oven temp. = 80°C for 5 min, ramp = 10°C/min, Column type = DB-1, Gas Flow Rate 2.0 mL/min) R_t = 14.27 min.

$\text{C}_6\text{H}_7\text{BrN}_2\text{O}_2$ calc. C 32.89 H 3.22 N 12.79
(219.1) found 32.90 3.17 12.85

¹H-NMR (250 MHz, CDCl_3): δ = 3.85 (s, 3H); 3.91 (s, 3H); 7.67 (s, 1H).

Methyl 2,4-Dibromo-1-methyl-5-imidazolecarboxylate (8):

Method A: To ester **18** (4.15 g, 0.03 mol) in $\text{CBrCl}_3/\text{CCl}_4$ (1:1, 120 mL) is added NBA (12.42 g, 0.09 mol) and AIBN (0.25 g, 1.5 mmol) at 50°C with vigorous stirring. After 60 h at 50°C the solution is evaporated, the residue is taken up in water (100 mL) and the pH adjusted to 8 with solid NaHCO_3 . The solution is extracted with CH_2Cl_2 (3 \times 50 mL), and the combined organic layers are dried (Na_2SO_4) and evaporated to give **8** as a light yellow solid; yield: 7.25 g (81%); mp 96–101°C (hexane); GC/MS (oven temp. = 80°C for 5 min, ramp = 10°C/min, column type = DB-1, gas flow rate 2.0 mL/min) indicates besides **8**, 14% of mixed chlorobromo compounds as impurities; R_t (**8**) = 16.84 min; R_t (impurities) = 15.49 and 15.61 min.

GC/MS: m/z (%) for **8** = 296 (M^+ , 51, ⁷⁹Br ⁷⁹Br); 298 (M^+ , 100, ⁷⁹Br ⁸¹Br); 300 (M^+ , 51, ⁸¹Br ⁸¹Br).

$\text{C}_6\text{H}_6\text{Br}_2\text{N}_2\text{O}_2$ calc. C 24.18 H 2.03 N 9.40
(298.1) found 24.70 2.05 9.55

IR (CCl_4): ν = 3440, 2980, 1725, 1505, 1480, 1450, 1415 cm^{-1} .

¹H-NMR (500 MHz, CDCl_3): δ = 3.910 (s, 3H); 3.912 (s, 3H).

¹³C-NMR (CDCl_3): δ = 32.0, 51.83, 122.5, 123.12, 125.7, 159.03.

Method B: To a stirred solution of ester **18** (1.00 g, 7.09 mmol) in pure fractionally distilled CHBr_3 (25 mL) is added NBA (2.93 g, 21.27 mmol) at 50°C. After 36 h at 50°C, the mixture is cooled to 20°C and hexane (10 mL) and H_2O (20 mL) are added and the layers are separated. The organic layer is washed with H_2O (2 \times 20 mL), the aqueous layers are back-extracted with a EtOAc/hexane mixture (1:1.2, 25 mL), and the combined organic layer is dried (Na_2SO_4) and evaporated to a light

yellow solid. Gravity column chromatography on silica (20 g, eluent: EtOAc/hexane, 1:1) affords monobromo ester **21**; yield: 390 g (25%), and dibromo ester **8**; yield: 1.05 g (50%) as white solids.

Recovered monobromo ester when subjected to identical conditions gives a mixture of dibromo ester **8** (60%) and monobromo ester **21** (28%).

Method C: To a stirred solution of ester **7** (50 mg, 0.23 mmol) in CCl₄ (12 mL, dried over activity I alumina) is added NBS (100 mg, 0.46 mol). The mixture is stirred for 5 d, adding portions of NBS (100 mg) after the second and fourth day. Evaporation of the solvent and subsequent LPLC, eluting with CHCl₃, affords dibromo ester **8** as a white solid; yield: 60 mg (85%).

1-Methyl-4-imidazolecarboxylic Acid (19):

A mixture of **16** (850 mg, 5 mmol) and *N,N*-dimethylacetamide (25 mL) is heated at 180°C for 3 h. The mixture is evaporated and the residue triturated with benzene followed by recrystallization from EtOH to give **19**; yield: 470 mg (75%); mp 245–246°C (Lit.¹³ mp 246–247°C, dec).

Methyl 1-Methyl-4-imidazolecarboxylate (20):

A mixture of acid **19** (400 mg, 3.1 mmol) in MeOH (25 mL) is cooled in an ice bath and the solution saturated with dry HCl, followed by refluxing for 12 h. After cooling, HCl is removed by a rapid stream of N₂, solid NaHCO₃ is added and the solution evaporated. The residue is suspended in water (15 mL), and extracted with CHCl₃ (3 × 15 mL). The combined organic layer is dried (MgSO₄) and evaporated and the residue kept at 25°C/0.0 mbar for 12 h to remove volatile impurities, then at 60°C/0.0 mbar for 2 h to afford **20** as a white solid; yield: 390 mg (90%); mp 98–101°C (Lit.¹⁵ mp 97–98°C); HPLC, R_t = 2.8 min.

GC/MS: (oven temp. = 110°C for 5 min, ramp-20°C/min, column type = DB-5, gas flow rate 2.0 mL/min) R_t = 5.75 min; *m/z* (%) = 140 (M⁺, 22); 109 (100).

¹H-NMR (250 MHz, CDCl₃): δ = 3.73 (s, 3 H); 3.87 (s, 3 H); 7.44 (d, 1 H, *J* = 1.3 Hz); 7.57 (d, 1 H, *J* = 1.3 Hz).

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