Convenient synthesis of polybrominated imidazole building blocks

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Abstract
The synthesis of the hitherto unknown 1-phenylamino-4,5-dimethylimidazole derivatives 3, 4 and 5 is shown and a bromination study is described by using N-bromosuccinimide. It is extremely remarkable that under mild but nevertheless free radical reaction conditions, even by using drastically increasing amounts of NBS (up to 8 eq.) the bromination provides regioselectively in very good yields only the corresponding 2-bromoimidazoles, whereas no side chain bromination to the 4- and 5-methyl groups is observed. However, under more drastic reaction conditions, reflux in CCl₄, polybromination takes place and polybrominated imidazole building blocks are formed in good yields.

Keywords: Acetylation, bromination, N-bromosuccinimide, imidazoles, regioselectivity

Introduction
Heterocyclic compounds are rich sources of diverse physical, chemical, and biological properties. In medicinal chemistry they are commonly used as templates to design biologically active agents. Imidazole-based heterocyclic molecules play important roles in various biochemical processes. Therefore, the imidazolyl moiety is being used as a building block in developing new drugs. Moreover, imidazole derivatives have wide range applications in coordination chemistry, organometallic catalysis, and asymmetric catalysis. There are several reports for the synthesis and functionalization of the imidazole moiety. The most efficient synthetic routes to polyfunctional compounds involve halogen-metal exchange on iodo- or bromoimidazoles. In addition, bromination of aromatic and heteroaromatic compounds is an important reaction in synthetic organic chemistry. On the other hand, brominated and polybrominated arenes and heteroarenes are useful as pharmaceuticals, agrochemicals, flame retardants and specialty chemicals. Consequently, the bromination of the imidazole ring is of high synthetic interest and efforts have to be made to develop this reaction. Singh and co-workers have disclosed the monobromination of alkyl activated nitroimidazoles using the
DMF-Br₂ complex and very recently, the same complex was used for large scale preparation of polybrominated imidazoles. In addition, some highly substituted imidazolones were converted to 2-bromimidazoles by reflux with phosphorus oxychloride in toluene for 6 h. The exhaustive bromination of a variety of benzimidazoles with bromine and of some tetrahydrobenzimidazoles with NBS at –10 °C has also been studied recently. The need for an easy access to brominated imidazoles aiming at the functionalization of the imidazole ring as well as of the methyl groups of substituted imidazoles led us to the synthesis of 4,5-dimethyl substituted imidazole derivatives and to the study of their nuclear versus side chain bromination. It should also be noticed that only in a few cases, the rates of nuclear versus side chain bromination have been compared within the same substrate, especially when heterocyclic rings are concerned. Moreover, whereas nuclear bromination has been observed under apparent radical conditions, side chain bromination has not been reported as a side reaction of electrophilic substitution.

Results and Discussion

Our synthetic approach is depicted in Scheme 1. 4,5-Dimethyl-1-(phenylamino)-1H-imidazole-2(3H)-thione (1) was prepared according to a known procedure by the reaction of 3-chloro-2-butanone with potassium thiocyanate and phenylhydrazine. However, a careful study of its NMR spectrum revealed that in CDCl₃ solution compound tautomerizes between forms and . More specifically, the NH ring proton of resonates at , whereas the SH proton of resonates at , their ratio being 2:1. Compound 1 was desulfurized to the imidazole with . Methylation of the phenylamino substituent proceeded smoothly with sodium hydride and methyl iodide in THF and the N-methylanilinoimidazole 3 was isolated in 65% yield.

On the contrary, when acetylation of the phenylamino substituent was attempted by the use of acetyl chloride in the presence of triethylamine, the hitherto unknown very interesting acetylated N-oxide 4 was isolated in 59 % yield (Scheme 1). The same N-oxide 4 was isolated in 61 % yield, when dimethylaminopyridine (DMAP) was used in addition to triethylamine, whereas by using acetyl chloride in the presence of pyridine the expected acetylated product 5 was isolated in 65 % yield. Finally, by using acetic anhydride in chloroform a mixture of compounds 4 and 5 was formed in 29% and 30 % yield, respectively.

The formation of compound 4 can be explained by assuming a nucleophilic attack of water at 2-position during purification of 5 on column chromatography.

To investigate the bromination of the N-methyl- and N-acetyl- anilinoimidazoles 3 and 5, we have proceeded systematically and comparatively using different brominating reagents and conditions. Thus, the N-methylanilinoimidazole derivative 3 was treated with NBS in carbon tetrachloride solution over a 200W light bulb and the results are presented in Scheme 2 and in Table 1. By using 1.2–6.0 equivalents of NBS at r.t. after 12 h only the 2-bromimidazole 6 was isolated in 88–93% yield (Table 1: entries 1 and 2). When the same reaction was repeated under
reflux after a short reaction time, namely 5 min, a mixture of the 2-bromoimidazole 6 and of the 4′-bromophenyl-2-bromoimidazole derivative 7 was formed, compound 6 being completely transformed to 7 during the next 15 min after addition of 1 eq. more NBS (78% yield) (Table 1: entries 3 and 4). These results can be rationalized by accepting that electrophilic nucleous bromination overrides methyl bromination even under free radical conditions.

\[
\text{PhNHNNH}_2 + \text{KSCN} + \text{CH}_3\text{COCCHClCH}_3
\]

\[
\text{CH}_3\text{COOH} \rightarrow \text{H}_2\text{O}_2 \rightarrow \text{CH}_3\text{COOH}
\]

\[
\text{HN}^-\text{N}^-\text{N}^-\text{HN}^-\text{Ph}
\]

\[
\text{HN}^-\text{N}^-\text{N}^-\text{SH}
\]

Scheme 1

By increasing the amount of NBS (2.5 up to 5 eq.), bromination of the methyl groups also takes place and mixtures of polybrominated compounds are formed (7, 8, 9) (Table 1: entry 5). However, by using 6 eq. of NBS mainly the tribromo derivative 8 was formed after 20 min, which was completely converted to the tetrabromo derivative 9 after 1 h (65% yield) (Table 1: entries 6 and 7) proving thus, that for the free radical bromination of the methyl groups a combination of light/temperature is required. The same tetrabromo derivative 9 was formed (57% yield) by using benzoylperoxide as radical initiator (Table 1: entry 8). Next, 2,2′-azobisisobutyronitrile (AIBN) was used whereupon, when \(N\)-methylaminooimidazolone 3 was treated with 1.2 eq. of NBS in carbon tetrachloride, at ambient temperature, the dibromo derivative 7 was regioselectively formed in 42% yield. The same regioselectivity was observed even by increasing the amount of NBS to 8 eq. in the presence of AIBN, whereupon 7 was again formed as the only product at ambient temperature (74% yield) (Table 1: entries 9 and 10). However, when the reaction was repeated under drastically free radical conditions, namely under reflux in the presence of AIBN with 2.5 up to 5.0 eq. of NBS, the regioselectivity diminishes and a mixture of compounds 7, 8 and 9 was formed (Table 1: entry 11). Finally, when a blank experiment was performed at room temperature by using 1.2 equivalents of NBS only 6 was
isolated in 91\% yield after 30 h. By increasing the amount of NBS to 8.0 equivalents 6 was again formed along with traces of the dibromo derivative 7 after 5 h at r.t. (Table 1: entries 12 and 13), indicating thus that the presence of AIBN speeds up the formation of 7.

Scheme 2

Table 1. Various conditions and products during the bromination of 3 in CCl₄ by NBS

| Entry | Radical initiator | NBS equiv. | Time (min) ⁴ | Temperature | Product (%)
|-------|------------------|------------|--------------|-------------|-----------
| 1     | hv               | 1.2        | 12 h         | r.t.        | 6 (88)    |
| 2     | hv               | 6.0        | 12 h         | r.t.        | 6 (93)    |
| 3     | hv               | 1.2        | 5            | reflux      | 6+7 b     |
| 4     | hv               | 2.2        | 20           | reflux      | 7 (78)    |
| 5     | hv               | 2.5–5.0    | 45           | reflux      | 7+8+9 b   |
| 6     | hv               | 6.0        | 20           | reflux      | 8+9 b     |
| 7     | hv               | 6.0        | 60           | reflux      | 9 (65)    |
| 8     | (PhCOO)₂         | 6.0        | 60           | reflux      | 9 (57)    |
| 9     | AIBN             | 1.2        | 24 h         | r.t.        | 7 (42)    |
| 10    | AIBN             | 8.0        | 5            | r.t.        | 7 (74)    |
| 11    | AIBN             | 2.5–5.0    | 45           | reflux      | 7+8+9 b   |
| 12    | none             | 1.2        | 30 h         | r.t.        | 6 (91)    |
| 13    | none             | 8.0        | 5            | r.t.        | 6+7 (trace) |

⁴ Or in h, as indicated. b Identified by ¹H NMR of the crude mixture.
Next, N-acetylanilinoimidazole 5 was treated with NBS under reflux in carbon tetrachloride solution over a 200 W light bulb and the results are presented in Scheme 3. By using only 1.2 eq. of NBS after a short reaction time, namely 5 min, only 2-bromoimidazole 10 was formed in 71% yield. By increasing the amount of NBS, bromination of the methyl groups also takes place and mixtures of polybrominated compounds are formed. However, by using 7 eq. of NBS only the pentabromo derivative 11 was formed after 1 h (60% yield). Finally, the 2-bromoimidazole derivative 10 was again isolated in 65% yield by using AIBN and 1.2 eq. of NBS at ambient temperature. It should also be mentioned that the N-substituent on the phenylamino group controls the bromination on the phenyl ring. Thus, in the case of an activating methyl group, phenyl bromination is also observed, whereas in the presence of an electron withdrawing group the phenyl ring is deactivated.

Since there is little methodology available for regioselective functionalization of imidazoles at the C-2 position, we feel that this method for the regioselective bromination of imidazoles may find application in the synthesis of imidazole containing natural products.

All products were unequivocally characterized by MS and NMR spectra (1H, 13C, H–H COSY, C–H COSY and C–H COLOC). The assignment of signals corresponding to C(4), C(5) as well as to CH3-4 and CH3-5 is supported by the NOESY cross signals between the 5-methyl protons with the aromatic ones as well by the fact that carbons in position 5 have sterically induced upfield shifts.

Regarding the structure of compound 4, its molecular formula is supported from the elemental analysis and mass spectra. The presence of an acetyl moiety introduced to the phenylamino group was unequivocally established from the NMR spectra (see experimental) and also from the carbonyl absorption in the IR spectrum at 1666 cm−1. Concerning the hydroxyl group it appears in the 1H NMR as a broad singlet at δ 12.38, forming most probably a hydrogen
bond with the adjacent carbonyl oxygen. This carbonyl carbon resonates at 161.3 ppm, whereas the corresponding carbon of starting material 2 resonates at 135.4.

Concerning the structure of compound 8, the position of the third bromine was unequivocally established from the $^1$H NMR of the 5-CH$_2$Br group which appears as an AB system (doublet of doublets) at $\delta$ 4.26 and 4.43 with $J = 11.5$ Hz, due to restricted rotation being in the vicinity of the N-1 substituent. Analogous behaviour is observed in the case of compound 9, where the 5-CH$_2$Br group appears as an AB system with $J = 12.2$ Hz, whereas the 4-CH$_2$Br group, suffering no restricted rotation appears as a singlet.

By the identification of compound 8 the bromination sequence of 3 was unequivocally established as follows: Initial bromination occurs at position C-2 and is followed by the bromination at position C-4'. Subsequent bromination takes place at the more crowded 5-CH$_3$ group and finally the 4-CH$_3$ is brominated.

In summary, the synthesis of the hitherto unknown 1-phenylamino-4,5-dimethylimidazole derivatives 3, 4 and 5 is described and a bromination study leading to the regioselective functionalization of imidazoles at the C-2 position, which may find application in the synthesis of imidazole containing natural products, is presented. Furthermore, it is established that the N-substituent on the phenylamino group controls the bromination on the N-phenyl ring. Under more drastic reaction conditions polybromination takes place and polybrominated imidazole building blocks are formed in good yields. For all new compounds full assignment of proton and carbon NMR chemical shifts was achieved. The reactivity of the polybromoimidazole scaffolds is now under investigation.

Experimental Section

General Procedures. Melting points were measured on a Kofler hot-stage and are uncorrected. Column chromatography was carried out using Merck silica gel (70-230 mesh). Petroleum ether refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 MHz for $^1$H and 75 MHz for $^{13}$C, respectively, using CDCl$_3$ as solvent. The chemical shifts are expressed in $\delta$ values (ppm) relative to TMS as internal standard for $^1$H and relative to TMS (0.00 ppm) or to CDCl$_3$ (77.05 ppm) for $^{13}$C NMR spectra. Coupling constants $^nJ$ are reported in Hz. Low resolution electron impact mass spectra (EIMS) were obtained on a VG TS-250 instrument and elemental analyses performed with a Perkin-Elmer 2400-II CHN analyzer.

2,3-Dihydro-4,5-dimethyl-1-phenylamino-1H-imidazole-2-thione (1)
The compound was synthesized in 70% yield according to a known procedure. $^{18}$ Mp 229–231 °C (lit. $^{18}$ 230–232 °C). $^1$H NMR $\delta$ ppm: 2.04 (s, 3H, 5-CH$_3$), 2.09 (s, 3H, 4-CH$_3$), 4.78 (br s, 0.333H, SH), 6.66 (d, $J = 8.4$ Hz, 2H, 2’,6’), 6.96 (t, $J = 7.4$ Hz, 1H, 4’), 7.11 (br s, 1H, PhNH), 7.25 (dd, $J_1 = 8.4, J_2 = 7.4$ Hz, 2H, 3’,5’), 11.25 (br s, 0.667H, NH). $^{13}$C NMR $\delta$ ppm: 7.2 (5-CH$_3$), 8.5 (4-
CH$_3$), 112.5 (2′,6′), 117.1 (5), 120.0 (4′), 121.9 (4), 128.2 (3′,5′), 145.9 (1′), 158.3 (2). EIMS: $m/z$ (%) 219 (M$^+$, 100), 203 (50), 186 (70), 177 (25), 161 (15), 151 (65), 136 (28), 128 (30), 93 (30).

**4,5-Dimethyl-1-phenylamino-1H-imidazole (2).** The compound was synthesized in 80% yield according to a known procedure.$^{19}$ Mp 178–180 °C (lit.$^{19}$ 175–177 °C). $^1$H NMR δ ppm: 7.97 (s, 3H, NH), 7.50 (s, 1H, 2). 13C NMR δ ppm: 107.1 (5), 120.0 (4′), 121.9 (4), 128.2 (3′,5′), 145.9 (1′). EIMS: $m/z$ (%) 219 (M$^+$, 100), 203 (50), 186 (70), 177 (25), 161 (15), 151 (65), 136 (28), 128 (30), 93 (30).

To a suspension of compound 2 (0.094 g, 0.5 mmol) in dry tetrahydrofuran (20 mL) at 0 °C sodium hydride (0.04 g of 60% in oil, 1.1 mmol) was added. Salt formation was allowed to proceed at ambient temperature for 30 min, methyliodide (0.15 g, 1.0 mmol) was then added and the solution was stirred for 1.5 h. Water was added, the organic layer was washed with water, dried (Na$_2$SO$_4$) and concentrated. The methylated product was crystallized by the addition of petroleum ether as a yellow solid, 0.065 g, 65% yield. Mp 78–80 °C (CH$_2$Cl$_2$-petroleum ether). $^1$H NMR δ ppm: 1.97 (s, 3H, 5-CH$_3$), 2.21 (s, 3H, 4-CH$_3$), 3.38 (s, 3H, N-CH$_3$), 6.47 (d, $J = 8.0$ Hz, 2H, 2′,6′), 6.91 (t, $J = 7.5$ Hz, 1H, 4′), 7.25 (dd, $J_1 = 8.0$, $J_2 = 7.5$ Hz, 2H, 3′,5′), 7.50 (s, 1H, 2). 13C NMR δ ppm: 112.5 (2′,6′), 120.3 (4′), 123.5 (5), 129.3 (3′,5′), 133.8 (2), 148.9 (1′). EIMS: $m/z$ (%) 201 (M$^+$, 82), 186 (5), 159 (21), 118 (30), 106 (100). Anal. Calcd for C$_{12}$H$_{15}$N$_3$ (201.27): C, 71.61; H, 7.51; N, 20.88.

**Reaction of 2 with CH$_3$COCl/Et$_3$N. Formation of 1-(acetylphenylamino)-1,3-dihydro-3-hydroxy-4,5-dimethyl-2H-imidazol-2-one (4)**

Acetylchloride (0.10 g, 1.3 mmol) was added dropwise to a solution of 2 (0.094 g, 0.5 mmol) and dry triethylamine (0.060 g, 0.59 mmol) in anhydrous methylene chloride (3mL). The reaction mixture was stirred at room temperature for 48 h, and then poured into water. The organic layer was washed with 5% NaHCO$_3$ solution, with 5% HCl solution, finally with water, and then was dried over Na$_2$SO$_4$. The solvent was then removed and the residue was purified on a silica gel column using petroleum ether-EtOAc (1:1) as eluent, whereupon compound 4 was isolated as white crystals, 0.078 g, 59%, mp 205–207 °C (ethanol). $^1$H NMR δ ppm: 2.01 (s, 3H, 5-CH$_3$), 2.11 (s, 3H, 4-CH$_3$), 2.16 (s, 3H, COCH$_3$), 7.23 (m, 1H, 4′), 7.36 (m, 2H, 3′,5′), 7.55 (d, $J = 9.0$ Hz, 2H, 2′,6′), 12.38 (br s, 1H, OH). $^{13}$C NMR δ ppm: 8.4 (br, 5-CH$_3$), 9.3 (4-CH$_3$), 25.6 (br, COCH$_3$), 119.9 (5), 121.3 (4), 123.2 (2′,6′), 126.8 (4′), 128.9 (3′,5′), 139.5 (1′), 161.3 (2), 170.8 (C=O). EIMS: $m/z$ (%) 261 (M$^+$, 55), 246 (48), 203 (20), 125 (100). Anal. Calcd for C$_{13}$H$_{15}$N$_3$O$_3$ (261.28): C, 59.76; H, 5.79; N, 16.08. Found: C, 59.59; H, 5.67; N, 16.13.

**Reaction of compound 2 with CH$_3$COCl/Et$_3$N/DMAP. –Formation of compound 4**

Acetylchloride (0.270 g, 3.4 mmol) was added dropwise to a solution of 2 (0.187 g, 1.0 mmol), dry triethylamine (0.05 g, 0.50 mmol) and dimethylaminopyridine (DMAP) (0.06 g, 0.4 mmol) in anhydrous methylene chloride (3 mL). The reaction mixture was stirred at room temperature for 48 h, and then worked up as above to give compound 4, 0.159 g, 61% yield.
Reaction of compound 2 with CH₃COCl/pyridine.– Formation of 4,5-dimethyl-N-phenylacetylamiido-1H-imidazole (5)

To an ice cooled solution of 2 (0.374 g, 2.0 mmol) in anhydrous methylene chloride (3mL) dry pyridine (0.158 g, 2.0 mmol) was added followed by the dropwise addition of acetylchloride (0.5 g, 2.6 mmol). The reaction mixture was stirred at room temperature for 48 h, and then poured into water. The organic layer was washed with 5% NaHCO₃ solution, with 5% HCl solution, finally with water, and then was dried over Na₂SO₄. The solvent was then evaporated under reduced pressure. The residue was crystallized, by addition of methylene chloride and ether, to give white crystals of compound 5 in 65% yield. Mp 118–120 °C (methylene chloride-ether). IR (cm⁻¹): 1694 (C=O). ¹H NMR δ ppm: 2.02 (s, 3H, COCH₃), 2.07 (s, 3H, 5-CH₃), 2.19 (s, 3H, 4-CH₃), 7.20–7.32 (m, 3H, 3΄,4΄,5΄), 7.35–7.45 (m, 2H, 2΄,6΄), 7.60 (s, 1H, 2). ¹³C NMR δ ppm: 13.0 (4-CH₃), 13.3 (4-CH₃), 39.8 (N-CH₃), 111.8 (2΄,6΄), 117.0 (2), 120.2 (4΄), 126.3 (5), 129.4 (3΄,5΄), 133.5 (4), 147.0 (1΄). Anal. Calcd for C₁₃H₁₅N₃O (229.28): C, 68.10; H, 6.59; N, 18.33. Found: C, 68.29; H, 6.50; N, 18.13.

However, when the reaction mixture is purified on a silica gel column using petroleum ether-EtOAc (1:1) as eluent, compound 5 is partially transformed to 4.

Acetylation of 2 with (CH₃CO)₂O/CHCl₃

Acetic anhydride (0.174 g, 1.3 mmol) was added dropwise at 5 °C to a solution of 2 (0.94 g, 0.5 mmol) in anhydrous chloroform (10 mL). The reaction mixture was stirred at room temperature for 48 h, and then poured into water. The organic layer was washed with 5% NaHCO₃ solution, with 5% HCl solution, finally with water, and then was dried over Na₂SO₄. By TLC and ¹H–NMR of the crude reaction mixture it was established that an approximately 1:1 mixture of 4 and 5 was formed.

Bromination of 3 with NBS and light

A magnetically stirred mixture of compound 3 (0.201 g, 1.0 mmol) and NBS (0.214 g, 1.2 mmol) in anhydrous CCl₄ (15 mL) was irradiated by a 200 W light bulb at r.t. for 12 h. The end of the reaction was monitored by TLC because with longer irradiation times decomposition of the reaction products is observed. The succinimide which was formed was removed by filtration. Concentration of the filtrate was followed by purification by column chromatography on silica gel using a mixture of petroleum ether-EtOAc (4:1) as eluent to afford.

2-Bromo-N-phenyl-N-4,5-trimethyl-1H-imidazole-1-amine (6). White solid, 0.28 g; yield 88%; mp 85–87°C. ¹H NMR δ ppm: 1.99 (s, 3H, 5-CH₃), 2.17 (s, 3H, 4-CH₃), 3.39 (s, 3H, N-CH₃), 6.44 (d, J = 8.7 Hz, 2H, 2΄,6΄), 6.90 (t, J = 7.5 Hz, 1H, 4΄), 7.26 (m, 2H, 3΄,5΄). ¹³C NMR δ ppm: 8.7 (5-CH₃), 13.3 (4-CH₃), 39.8 (N-CH₃), 111.8 (2΄,6΄), 117.0 (2), 120.2 (4´), 126.3 (5), 129.4 (3΄,5΄), 133.5 (4), 147.0 (1΄). Anal. Calcd for C₁₁H₁₂BrN₃ (266.14): C, 49.64; H, 4.54; N, 15.79. Found: C, 49.52; H, 4.64; N, 15.88.

When the same reaction was repeated under irradiation for 12 h at r.t. with 6.0 mmol NBS again only compound 6 was isolated in 93% yield. When the same reaction was repeated with 1.2 mmol NBS under irradiation and reflux, after 5 min a mixture of compound 6 and of compound
7 was formed. When the same reaction was repeated with 2.2 mmol NBS under irradiation and reflux, after 20 min the \textit{2-bromo-N-(4-bromophenyl)-N,4,5-trimethyl-1H-imidazole-1-amine (7)} was formed. Yellow solid, 0.28 g; yield 78\%, mp 101–103°C. $^1$H NMR δ ppm: 2.00 (s, 3H, 5-CH$_3$), 2.20 (s, 3H, 4-CH$_3$), 3.38 (s, 3H, N-CH$_3$), 6.32 (d, $J = 9.0$ Hz, 2H), 7.35 (d, $J = 9.0$ Hz, 2H). $^{13}$C NMR δ ppm: 8.4 (5-CH$_3$), 12.9 (4-CH$_3$), 40.0 (N-CH$_3$), 112.9 (4''), 113.6 (2'',6''), 116.8 (2), 126.3 (5), 132.4 (3'',5''), 133.4 (4), 146.3 (1''). EIMS: $m/z$ (%) 357/359/361 (M×, 38), 2278/280 (8), 237/239 (6), 199 (16), 184/186 (100), 174/176 (32), 155/157 (25), 105 (65). Anal. Calcd for C$_{12}$H$_{13}$Br$_2$N$_3$ (359.06): C, 40.14; H, 3.65; N, 11.70. Found: C, 40.38; H, 3.74; N, 11.88.

When the same reaction was repeated with 6 mmol NBS, under reflux and irradiation for 20 min, the \textit{2-bromo-5-bromomethyl-N-(4-bromophenyl)-N,4-dimethyl-1H-imidazole-1-amine (8)} was mainly formed. $^1$H NMR δ ppm: 2.27 (s, 3H, 4-CH$_3$), 3.49 (s, 3H, N-CH$_3$), 4.26 (d, $J = 11.5$ Hz, 1H, 5-CH$_2$Br), 4.43 (d, $J = 11.5$ Hz, 1H, 5-CH$_2$Br), 6.34 (d, $J = 9.0$ Hz, 2H, 2'',6''), 7.36 (d, $J = 9.0$ Hz, 2H, 3'',5''). 13C NMR δ ppm: 17.3 (5-CH$_2$), 23.7 (4-CH$_2$), 40.4 (N-CH$_3$), 113.7 (4''), 114.0 (2'',6''), 126.0 (2), 129.2 (5), 132.5 (3'',5''), 136.8 (4), 145.9 (1''). Anal. Calcd for C$_{12}$H$_{11}$Br$_4$N$_3$ (516.85): C, 27.89; H, 2.15; N, 8.13. Found: C, 28.00; H, 2.04; N, 8.28. Due to the instability of compound 9 at higher temperature, it was not possible to measure the mp and ms.

\textbf{Bromination of compound 3 with NBS and (PhCOO)$_2$}

To a magnetically stirred mixture of compound 3 (0.201 g, 1.0 mmol) and NBS (1.068 g, 6.0 mmol) in anhydrous CCl$_4$ (15 mL) (PhCOO)$_2$ (0.048g, 0.2 mmol) was added and the mixture was refluxed for 1 h. The succinimide, which was formed, was removed by filtration. Concentration of the filtrate and purification afforded compound 9, 0.294 g, 57\% yield.

\textbf{Bromination of compound 3 with NBS and AIBN}

To a magnetically stirred mixture of compound 3 (0.201 g, 1.0 mmol) and NBS (0.214 g, 1.2 mmol) in anhydrous CCl$_4$ (15 mL) AIBN (0.043g, 0.2 mmol) was added and the mixture was stirred at room temperature for 24 h. The succinimide which was formed was removed by filtration. Concentration of the filtrate and purification by column chromatography on silica gel using a mixture of petroleum ether-EtOAc (4:1) as eluent afforded compound 7, 0.151 g, 42\% yield, along with unreacted starting material. Analogous results were obtained, when the reaction was repeated with 8.0 eq. of NBS for 5 h, whereupon compound 7 was again isolated as the only reaction product, 0.266 g, 74\% yield. However, when the reaction was repeated under reflux with 1.2–8.0 eq. of NBS mixtures of compounds 7, 8 and 9 were formed.

\textbf{Bromination of compound 3 with NBS}

A mixture of compound 3 (0.201 g, 1.0 mmol) and NBS (0.214 g, 1.2 mmol) in anhydrous CCl$_4$ (15 mL) was magnetically stirred for 30 h. The succinimide, which was formed, was removed by
filtration. Concentration of the filtrate and purification afforded compound 6 in 91% yield. When the same reaction was repeated with 8.0 mmol NBS for 5 h compound 6 containing an amount (approximately 5%) of compound 7 was formed.

**Bromination of compound 5 with NBS and light**

A magnetically stirred mixture of compound 5 (0.229 g, 1.0 mmol) and NBS (0.196 g, 1.1 mmol) in anhydrous CCl₄ (15 mL) was irradiated by a 100 W light bulb for 45 min. The end of the reaction was monitored by tlc, because with longer irradiation times decomposition of the products is observed. The succinimide, which was formed, was removed by filtration. Concentration of the filtrate and purification by column chromatography on silica gel using a mixture of petroleum ether-EtOAc (4:1) as eluent to afford:

**2-Bromo-4,5-dimethyl-N-phenylacetylamido-1H-imidazole (10).** 0.219 g, Yield 71%, mp 193–195 °C. ¹H NMR δ ppm: 2.01 (s, 3H, COCH₃), 2.09 (s, 3H, 5-CH₃), 2.19 (s, 3H, 4-CH₃), 7.25–7.28 (m, 5H, Ph). ¹³C NMR δ ppm: 8.8 (5-CH₃), 13.2 (4-CH₃), 22.1 (COCH₃), 117.8 (5), 121.6 (2’,6’), 125.7 (2), 126.6 (4’), 129.2 (3’,5’), 134.7 (4), 139.2 (1’), 170.3 (C=O). EIMS: m/z (%) 307/309 (M⁺, 16), 266/268 (12), 228 (24), 186 (90), 173/175 (18), 145 (32), 118 (100). Anal. Calcd for C₁₃H₁₄BrN₃O (308.17): C, 50.67; H, 4.58; N, 13.64. Found: C, 50.78 H, 5.54; N, 13.48.

When 2.0–5.0 eq. of NBS were used complicated mixtures of polybrominated imidazoles were formed. Finally, with 7.0 eq. of NBS and 1 h irradiation time only

**2-Bromo-4,5-bisdibromomethyl-N-phenylacetylamido-1H-imidazole (11).** 0.375 g, 60% yield, mp 150–152 °C. ¹H NMR δ ppm: 2.17 (br s, 3H, COCH₃), 6.58 (s, 1H, 5-CHBr₂), 7.03 (s, 1H, 4-CHBr₂), 7.33–7.50 (br m, 5H, Ph). ¹³C NMR δ ppm: 18.9 (br, 5-CH), 22.3 (COCH₃), 28.6 (4-CH), 122.5 (br, 2’,6’), 123.6 (5), 127.4 (2), 128.4 (4’), 129.7 (3’,5’), 138.6 (4), 140.0 (br, 1’), 168.8 (CO). EIMS: m/z (%) 619/621/623/625/627/629 (M⁺, 15)²², 540/542/544/546/548 (70), 92 (100). Anal. Calcd for C₁₃H₁₀Br₅N₃O (623.76): C, 25.03; H, 1.62; N, 6.74. Found: C, 24.89 H, 1.54; N, 6.58.

**Bromination reaction of compound 5 with NBS and AIBN**

To a magnetically stirred mixture of 5 (0.229 g, 1.0 mmol) and NBS (0.214 g, 1.2 mmol) in anhydrous CCl₄ (15 mL) AIBN (0.043 g, 0.2 mmol) was added and the mixture was stirred at room temperature for 24 h. The succinimide, which was formed, was removed by filtration. Concentration of the filtrate and purification by column chromatography on silica gel, using a mixture of petroleum ether-EtOAc (4:1) as eluent, afforded compound 10, 0.20 g, 65% yield.
References and Notes

22. The peak intensity refers to the higher peak of bromine containing ions.