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N-Methylation of Aromatic Amines and N-Heterocycles under Acidic Conditions with the TTT (1,3,5-Trioxane–Triethylsilane–Trifluoroacetic Acid) System

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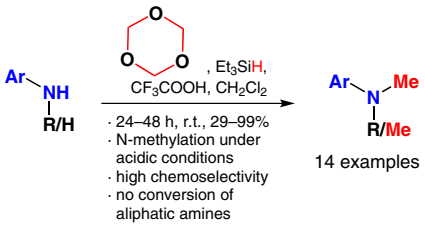

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Abstract A novel reductive N-methylation protocol under acidic conditions with the TTT (1,3,5-trioxane–triethylsilane–trifluoroacetic acid) system is disclosed. This method is highly specific for aromatic amines and several N-heterocycles (indoles and annulated analogues, phenoxazine, phenothiazine), insensitive to steric hindrance, and compatible with a wide range of functional groups. Further the N-methylation step can be combined with an in situ *N*-Boc deprotection. Compounds in which the nucleophilicity of the NH group is eliminated by protonation under the reaction conditions (aliphatic amines, azaarenes of noteworthy basicity) are inert. In several examples, it was demonstrated that the TTT system is complementary to other N-methylation protocols.

Key words N-methylation, aromatic amines, heterocycles, chemoselectivity, triethylsilane, trioxane

N-Methylation of primary, and even more important, secondary amines is a reaction of very high importance in natural products and drug synthesis, and numerous methods have been worked out for this conversion over the decades. Classical methods utilize methyl halides or dimethyl sulfate in the presence of acid scavengers for N-methylation of amines, or go through amide anions in the case of poorly nucleophilic substrates like anilines, pyrroles, azoles, and annulated analogues. These protocols typically give good yields, but are hampered by the volatility and toxicity of the methylation agents.[1] Moreover, overalkylation leading to quaternary ammonium salts or undesired C-alkylations at acidic positions[2] can take place under the required alkaline reaction conditions. Alternative methods include the use of the less toxic dimethyl carbonate, but with this reagent undesired C-methylations[1] as well as N- and C-methoxycarbonylations and formation of symmetrical ureas can occur.[3]

A mild alternative is the reductive N-methylation with formaldehyde and reducing agents like formic acid (Eschweiler–Clarke reaction[4]) and complex hydrides (sodium borohydride,[5] sodium cyanoborohydride in combination with mild Brønsted acids[6] or Lewis acids[7]). This method avoids the formation of quaternary ammonium salts, but proceeds significantly slower with aromatic amines.[5b] Primary amines give the *N*,*N*-dimethyl derivatives directly.[6] A reductive N-methylation of aliphatic and aromatic amines using paraformaldehyde in strongly acidic media has been published, but tedious adjustment of reaction conditions (reducing agent sodium borohydride or sodium cyanoborohydride; solvent mixtures containing acetic acid, trifluoroacetic acid, either neat or diluted with THF) was necessary, depending on the nature of the starting amines.[8] The reductive N-methylation of aliphatic and aromatic amines with formaldehyde can also be performed with decaborane as reducing agent.[9]

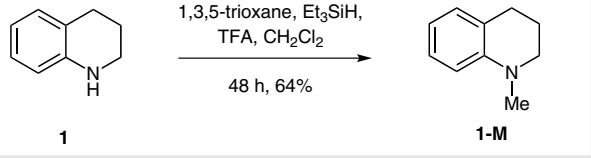
Selective monomethylation of primary amines can be achieved by conversion into *N*-formyl derivatives[10] or alkyl carbamates,[11] followed by reduction with lithium aluminum hydride. Indoles and related azaheterocycles are N-methylated upon heating with dimethylformamide dimethyl acetal.[12]

In continuation of our research on bioactive indole, β-carboline, and carbazole derivatives,[2,13] we required an improved method for selective N-methylation of the pyrrole-type NH function of these and related heteroarenes. This new protocol should avoid side reactions that occur under the commonly used reaction conditions. We were inspired by a report on the N-alkylation of aromatic amines and heteroarenes with acetals of aldehydes and triethylsilane[14] or other silanes[15] in the presence of trifluoroacetic acid (TFA). This method works well for acetals of both aliphatic[14] and aromatic aldehydes,[15] but has, to the best of our knowledge,

not yet been applied to the introduction of a methyl group. The organosilane-trifluoroacetic acid mixture is compatible with a broad range of functional and protective groups.[16]

1,3,5-Trioxane, the cyclic trimer of formaldehyde, was selected as precursor of the methyl group for a number of reasons: first, this compound has a promising acetal-like structure, further it is (unlike paraformaldehyde) readily soluble in organic solvents,[17] and (in contrast to commonly used formaldehyde solution) allows working under anhydrous conditions.

We intended to investigate a broad panel of aromatic and aliphatic amines, as well as heterocyclic compounds, and selected two compounds for an explorative analysis: the aromatic amine 1,2,3,4-tetrahydroquinoline (**1**) and its regioisomer 1,2,3,4-tetrahydroisoquinoline (**2**) as a secondary aliphatic amine. The first experiments clearly indicated that the aromatic amine **1** readily undergoes N-methylation to give **1-M** with a 1,3,5-trioxane–triethylsilane–trifluoroacetic acid (TTT) mixture, whereas the aliphatic amine **2** was recovered unchanged. Reaction conditions for the N-methylation of 1,2,3,4-tetrahydroquinoline were optimized systematically, and the following best conditions were identified: 3 equivalents of 1,3,5-trioxane, 10 equivalents of triethylsilane in a 1:2 trifluoroacetic acid–dichloromethane mixture under nitrogen atmosphere, room temperature, and 24 to 48 hours (TLC control). N-Methylated product **1-M** was obtained in 64% yield after 48 hours; no by-products were observed, and significant amounts of starting material were recovered (Scheme 1).



Scheme 1 N-Methylation of 1,2,3,4-tetrahydroquinoline (**1**) with the 1,3,5-trioxane–triethylsilane–trifluoroacetic acid (TTT) mixture

Figure 1 shows the outcome of further N-methylation experiments, in Figure 2 compounds are presented, which did not undergo N-methylation. The secondary aromatic amines diphenylamine, *N*-benzylaniline, and tetracaine gave the corresponding N-methylated products **3-M**, **4-M**, and **5-M** in 51–89% yields; once again no side-products were observed. The primary aromatic amine ethyl 4-aminobenzoate gave 57% of the *N*,*N*-dimethyl derivative **6-M2** and 37% of the monomethylated product **6-M1**, whereas 4-nitroaniline was converted into its *N*,*N*-dimethyl derivative **7-M** in almost quantitative yield, without affecting the nitro group. Sterically hindered 2,4,6-trichloroaniline was smoothly converted into the *N*,*N*-dimethyl derivative **8-M** (93% yield). Previous synthesis of **8-M** required refluxing the aniline with dimethyl sulfate in toluene, giving only 54% yield.[18]

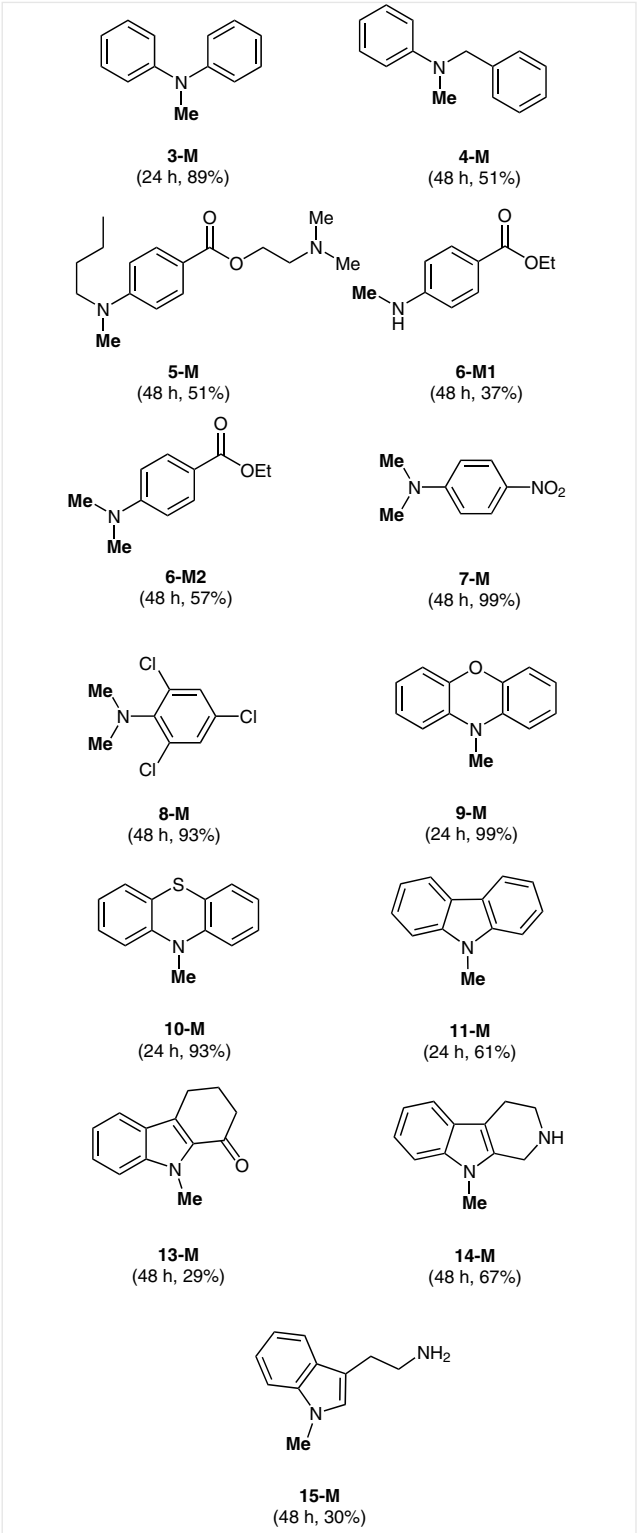


Figure 1 Products obtained by N-methylation with the TTT mixture. The introduced methyl groups are highlighted in bold, and reaction times and yields are given in parentheses. Both compounds **6-M1** and **6-M2** were obtained upon conversion of ethyl 4-aminobenzoate.

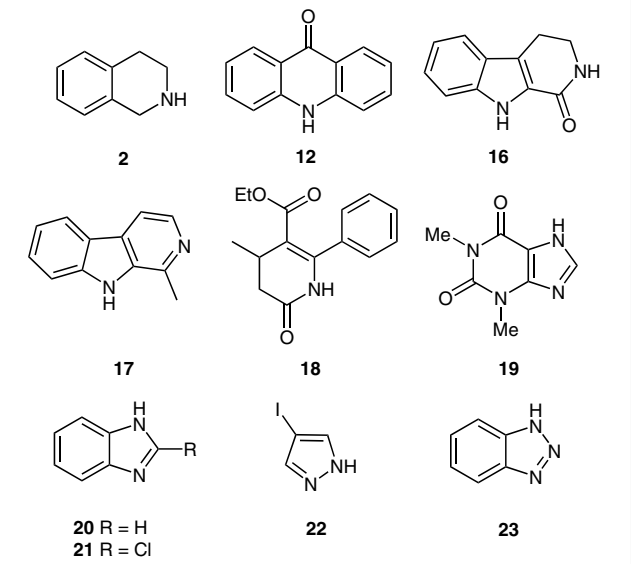


Figure 2 Compounds that did not undergo any conversion with the TTT system

In the series of heterocyclic substrates, phenoxazine and phenothiazine gave excellent yields of **9-M** and **10-M**, and *N*-methylcarbazole (**11-M**) was formed in 61% yield. In contrast, acridone (**12**) did not undergo any reaction.

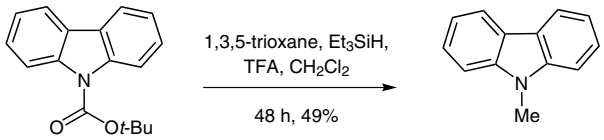
Next, indole-based compounds bearing additional functional groups were investigated. The N-methylated product **13-M** was obtained from 1-oxo-1,2,3,4-tetrahydrocarbazole in 29% yield, the only other substance in the reaction mixture was the starting material. This outcome is in strong contrast to attempts to perform the same conversion in a classical manner (sodium hydride, iodomethane), which gave only the 2,2,9-trimethyl derivative.[2] In accordance with the previous insights, 1,2,3,4-tetrahydro-β-carboline gave the N^9-methylated product **14-M**[19] in 67% yield, with no indication of a methylation of the secondary aliphatic amino group. In an analogous manner, exclusively the N^1-methylated derivative **15-M** (30% yield) was obtained from tryptamine. Most likely, in both cases the aliphatic amino groups are fully protonated in the strongly acidic reagent mixture,[15a] and thence protected from electrophilic attack by a reactive cationic intermediate generated from 1,3,5-trioxane.

This shows impressively that our TTT method is complementary to the standard reductive N-methylation protocol (aqueous formaldehyde, sodium cyanoborohydride), which gives clean conversions of **2** into 2-methyl-1,2,3,4-tetrahydroisoquinoline[19] and of tryptamine to *N*′,*N*′-dimethyltryptamine.[10] The results obtained with tryptamine are noteworthy, since we observed neither a reduction to the indoline[20] nor a Pictet–Spengler-type cyclization (which would result in a tetrahydro-β-carboline), as demonstrated for related arylethylamines, when treated with 1,3,5-trioxane and acid.[21]

Surprisingly, no conversion was achieved with both the 1-oxo-1,2,3,4-tetrahydro-β-carboline **16**[22] and harmane (**17**). We assume that in these examples the nucleophilicity of the pyrrole nitrogen is strongly diminished by cationic groups (protonated lactam carbonyl group, protonated pyridine ring) in direct conjugation to the nitrogen atom. We investigated another lactam substrate **18**,[23] but once again only recovered the starting material. The same outcome was observed for theophylline (**19**), not even traces of N-methylation product caffeine were found. Finally, other azaaromatic compounds were investigated, but no conversion of benzimidazole (**20**), 2-chlorobenzimidazole (**21**), 4-iodopyrazole (**22**), and benzotriazole (**23**) was observed.

Our attempts to extend this method to the N-ethylation of aromatic amines failed. Reaction of 1,2,3,4-tetrahydroquinoline (**1**) and paraldehyde (2,4,6-trimethyl-1,3,5-trioxane), the cyclic trimer of acetaldehyde, with triethylsilane in trifluoroacetic acid–dichloromethane gave a complex mixture of unidentifiable products.

Since trifluoroacetic acid is a major component of the TTT reagent mixture, we investigated whether the above mentioned N-methylation procedure can be combined with other trifluoroacetic acid-mediated reactions. *N*-Boc groups are cleanly cleaved by this acid; further, triethylsilane is known as a beneficial scavenger for *tert*-butyl cations in deprotections of *tert*-butyl esters and *tert*-butoxycarbonyl residues.[20b,24] Accordingly, *N*-Boc-carbazole (**11-Boc**)[25] was treated with the TTT mixture, and in fact *N*-methylcarbazole (**11-M**) was obtained in 49% yield in a one-pot deprotection–methylation sequence (Scheme 2).



Scheme 2 One-pot deprotection–methylation of *N*-Boc-carbazole (**11-Boc**)

In conclusion, we have worked out a novel reductive N-methylation protocol under acidic conditions with the TTT (1,3,5-trioxane–triethylsilane–trifluoroacetic acid) system. This method is highly specific for aromatic amines and several N-heterocycles (indoles and annulated analogues, phenoxazine, phenothiazine), insensitive to steric hindrance, and compatible with a wide range of functional groups. Further, the N-methylation step can be combined with an in situ *N*-Boc deprotection. Compounds in which the nucleophilicity of the NH group is eliminated by protonation under the reaction conditions (aliphatic amines, azaarenes of noteworthy basicity) are inert. In contrast to established reductive N-methylation protocols utilizing formaldehyde and complex hydrides in neutral or acidic solution,[5–9] this system shows no tendency for methylation of aliphatic

amines. In several examples, the TTT system is demonstrated as complementary to other N-methylation protocols, hence, we are confident that it will be a versatile tool for chemoselective N-methylations in the future.

Melting points were determined with a Büchi Melting Point B-540 (Büchi, Flawil, Switzerland) and are uncorrected. IR spectra were recorded with a Perkin Elmer FT-IR Spectrometer Paragon 1000 (Perkin Elmer, Waltham, USA) as a thin film on a NaCl plate or KBr discs. ^{1}H and ^{13}C NMR spectra were recorded with either Avance III HD 400 MHz Bruker BioSpin or Avance III HD 500 MHz Bruker BioSpin spectrometers (Bruker Biospin, Billerica, USA). Chemical shifts are given in ppm. EI mass spectra were recorded at an ionization energy of 70 eV either with a JMS GCmate II Jeol or a JEOL JMS-700 MStation (Joel, Peabody, USA). ESI mass spectra were recorded on a Thermo Finnigan LTQ FT at 4 kV (ThermoFisher Scientific, Waltham, USA). Purification by flash column chromatography (FCC) was performed using Silica Gel 60 (Merck, Darmstadt, Germany). HPLC purity analysis was performed on an Agilent 1100 Series apparatus with a G1311A QuatPump, a G1329A ALS autosampler, a G1316A ColComp column oven, and Agilent ChemStation Rev. B04.02 as software (Agilent, Santa Clara, USA). A G1315A DAD detector was set to 210 nm for detection. Agilent Poroshell 120 EC-C18 (3.0 × 100 mm; 2.7 µm) was used as column and a mixture of 80% MeCN, 19.8% H_2O, and 0.2% THF as mobile phase. Flow was 0.8 mL/min and column temperature 50 °C. Injection volume was 5 or 10 µL of a dilution of 100 µg/mL (sample in mobile phase).

N-Methylation of Aromatic Amines and N-Heterocycles; General Procedure

The N-containing substrate (1 mmol) and trioxane (270 mg, 3 mmol) were dissolved in CH_2Cl_2 (1.5 mL) under N_2 atmosphere. To this solution were added TFA (0.75 mL) and Et_3SiH (1.45 mL, 10 mmol). The reaction was monitored by TLC (eluent: see below). After 24 or 48 h (in case of incomplete conversion, after 24 h), aq 2 N NaOH (20 mL) solution was carefully added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo and the residue was purified by flash column chromatography (FCC).

1-Methyl-1,2,3,4-tetrahydroquinoline (1-M)

Prepared from 1,2,3,4-tetrahydroquinoline. Standard protocol workup after 48 h and purification by FCC [R_f = 0.5 (hexanes–EtOAc, 20:1)] gave the pure compound as a colorless oil; yield: 0.32 g (2.2 mmol, 64%); purity (HPLC): >99%; t_R = 2.7 min.

IR (film): 3065, 2927, 2862, 1602, 1507, 1321, 1208 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15–7.11 (m, 1 H), 7.02–6.99 (m, 1 H), 6.68–6.63 (m, 2 H), 3.28–3.25 (m, 2 H), 2.93 (s, 3 H), 2.82 (t, J = 6.5 Hz, 2 H), 2.07–2.00 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.9, 128.9, 127.1, 123.0, 116.3, 111.1, 51.4, 39.2, 27.9, 22.6.

MS (EI+): m/z (%) = 91.1 (21), 131.1 (23), 146.1 (100, [M – H]$^+$), 147.1 (87, [M]$^+$).

HRMS (EI+): m/z [M]$^+$ calcd for $C_{10}H_{13}N$: 147.1048; found: 147.1031.

N-Methyl-*N*-phenylaniline (3-M)

Prepared from diphenylamine. Standard protocol workup after 24 h and purification by FCC [R_f = 0.5 (hexanes–EtOAc, 10:1)] gave the pure compound as a colorless oil; yield: 0.35 g (1.9 mmol, 89%); purity (HPLC): >99%; t_R = 3.7 min.

IR (film): 3060, 3035, 2939, 2878, 1591, 1496, 1342, 1252, 1131 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.22 (m, 4 H), 7.03–6.98 (m, 4 H), 6.96–6.91 (m, 2 H), 3.29 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.1, 129.3, 121.4, 120.5, 40.3.

MS (EI+): m/z (%) = 77.1 (32), 104.1 (17), 168.1 (11), 183.2 (100, [M]$^+$).

HRMS (EI+): m/z [M]$^+$ calcd for $C_{13}H_{13}N$: 183.1048; found: 183.1036.

N-Benzyl-*N*-methylaniline (4-M)

Prepared from *N*-benzylaniline. Standard protocol workup after 48 h and purification by FCC [R_f = 0.6 (hexanes–EtOAc, 10:1)] gave the pure compound as a yellow oil; yield: 0.19 g (1.0 mmol, 51%); purity (HPLC): 96%; t_R = 4.6 min.

IR (film): 3061, 3026, 2894, 1599, 1506, 1451, 1354 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 2 H), 7.25–7.18 (m, 5 H), 6.77–6.72 (m, 2 H), 6.72–6.68 (m, 1 H), 4.51 (s, 2 H), 2.99 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.9, 139.1, 129.3, 128.7, 127.0, 126.8, 116.6, 112.5, 56.7, 38.6.

MS (EI+): m/z (%) = 91.0 (100), 120.1 (59), 197.1 (71, [M]$^+$).

HRMS (EI+): m/z [M]$^+$ calcd for $C_{14}H_{15}N$: 197.1204; found: 197.1198.

2-(Dimethylamino)ethyl 4-(*N*-Butyl-*N*-methylamino)benzoate (5-M)

Prepared from 2-(dimethylamino)ethyl 4-(*N*-butylamino)benzoate (tetracaine). Standard protocol workup after 48 h and purification by FCC [R_f = 0.2 (CH_2Cl_2 + 10% MeOH)] gave the pure compound as a colorless oil; yield: 0.27 g (1.0 mmol, 51%); purity (HPLC): >99%; t_R = 3.6 min.

IR (film): 2956, 2873, 2770, 1703, 1607, 1525, 1278, 1184, 1111 cm^{-1}.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.76–7.73 (m, 2 H), 6.54–6.51 (m, 2 H), 4.21 (t, J = 5.9 Hz, 2 H), 3.28–3.24 (m, 2 H), 2.88 (s, 3 H), 2.54 (t, J = 5.8 Hz, 2 H), 2.19 (s, 6 H), 1.50–1.43 (m, 2 H), 1.29–1.20 (m, 2 H), 0.85 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 167.1, 153.0, 131.7, 117.0, 110.9, 62.7, 58.6, 52.6, 46.1, 38.7, 29.5, 20.8, 14.3.

MS (EI+): m/z (%) = 58.1 (100), 164.1 (53), 207.1 (38), 278.2 (0.2, [M]$^+$).

HRMS (EI+): m/z [M]$^+$ calcd for $C_{16}H_{26}N_2O_2$: 278.1994; found: 278.1997.

Ethyl 4-(*N*-Methylamino)benzoate (6-M1) and Ethyl 4-(*N*,*N*-Dimethylamino)benzoate (6-M2)

Prepared from ethyl 4-aminobenzoate (benzocaine). Standard protocol workup after 48 h and purification by FCC [R_f = 0.5 and 0.3 (hexanes–EtOAc, 5:1)] gave ethyl 4-(methylamino)benzoate (**6-M1**) and ethyl 4-(dimethylamino)benzoate (**6-M2**) as white solids.

6-M1

Yield: 0.13 g (0.7 mmol, 37%); mp 62.4–62.7 °C; purity (HPLC): >99%; t_R = 1.8 min.

IR (KBr): 3383, 2962, 2936, 2903, 1680, 1602, 1538, 1276, 1174, 835 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90–7.86 (m, 2 H), 6.57–6.53 (m, 2 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 4.19 (s, 1 H), 2.88 (s, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.0, 152.9, 131.6, 118.7, 111.2, 60.3, 30.3, 14.6.

MS (EI+): *m*/*z* (%) = 106.1 (10), 134.1 (100), 151.1 (19), 179.1 (68, $[M]^+$).

HRMS (EI+): *m*/*z* $[M]^+$ calcd for $C_{10}H_{13}NO_2$: 179.0946; found: 179.0947.

6-M2

Yield: 0.21 g (1.1 mmol, 57%); mp 61.4–62.3 °C; purity (HPLC): >99%; t_R = 2.6 min.

IR (KBr): 2982, 2903, 2820, 1695, 1611, 1365, 1283, 1186, 1106 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93–7.89 (m, 2 H), 6.64–6.60 (m, 2 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 3.00 (s, 6 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.0, 153.2, 131.2, 117.3, 110.7, 60.1, 40.0, 14.5.

MS (EI+): *m*/*z* (%) = 148.1 (100), 164.1 (41), 193.2 (68, $[M]^+$).

HRMS (EI+): *m*/*z* $[M]^+$ calcd for $C_{11}H_{15}NO_2$: 193.1103; found: 193.1088.

***N*,*N*-Dimethyl-4-nitroaniline (7-M)**

Prepared from 4-nitroaniline. Standard protocol workup after 48 h and purification by FCC [R_f = 0.3 (hexanes–EtOAc, 5:1)] gave the pure compound as a yellow solid; yield: 0.31 g (1.9 mmol, 99%); mp 162.1–162.9 °C; purity (HPLC): >96%; t_R = 2.0 min.

IR (KBr): 3424, 2924, 1735, 1601, 1582, 1485, 1457, 1310, 1116 cm^{-1}.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 8.12–8.05 (m, 2 H), 6.65–6.60 (m, 2 H), 3.09 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 154.7, 137.1, 126.3, 110.6, 40.5.

MS (EI+): *m*/*z* (%) = 105.0 (18), 119.0 (26), 136.1 (28) 166.1 (100, $[M]^+$).

HRMS (EI+): *m*/*z* $[M]^+$ calcd for $C_8H_{10}N_2O_2$: 166.0742; found: 166.0738.

***N*,*N*-Dimethyl-2,4,6-trichloroaniline (8-M)**

Prepared from 2,4,6-trichloroaniline. Standard protocol workup after 48 h and purification by FCC [R_f = 0.7 (hexanes)] gave the pure compound as a colorless oil; yield: 0.40 g (1.8 mmol, 93%); purity (HPLC): >99%; t_R = 10.4 min.

IR (film): 3054, 2986, 1421, 1265, 739, 705 cm^{-1}.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.30–7.28 (m, 2 H), 2.85 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 145.8, 136.3, 130.4, 129.2, 42.2.

MS (EI+): *m*/*z* (%) = 223.0 (49, $[M]^+$), 222.0 (100, $[M - H]^+$).

HRMS (EI+): *m*/*z* $[M]^+$ calcd for $C_8H_8Cl_3N$: 222.9722; found: 222.9722.

10-Methyl-10*H*-phenoxazine (9-M)

Prepared from 10*H*-phenoxazine. Standard protocol workup after 24 h and purification by FCC [R_f = 0.6 (hexanes–EtOAc, 20:1)] gave the pure compound as a white to pale violet solid; yield: 0.37 g (1.9 mmol, 99%); mp 26.5–27.1 °C; purity (HPLC): >99%; t_R = 3.4 min.

IR (KBr): 3063, 2882, 1592, 1486, 1362, 1268, 1217 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.90–6.84 (m, 2 H), 6.75–6.70 (m, 4 H), 6.54 (d, *J* = 7.9 Hz, 2 H), 3.05 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.7, 135.1, 123.9, 121.0, 115.4, 111.5, 31.0.

MS (EI+): *m*/*z* (%) = 127.1 (6), 182.1 (100), 197.1 (63, $[M]^+$).

HRMS (EI+): *m*/*z* $[M]^+$ calcd for $C_{13}H_{11}NO$: 197.0841; found: 197.0831.

10-Methyl-10*H*-phenothiazine (10-M)

Prepared from 10*H*-phenothiazine. Standard protocol workup after 24 h and purification by FCC [R_f = 0.6 (hexanes–EtOAc, 20:1)] gave the pure compound as a white solid; yield: 0.41 g (1.9 mmol, 95%); mp 100.5–101.7 °C; purity (HPLC): 99%; t_R = 4.0 min.

IR (KBr): 3058, 2968, 2888, 1592, 1568, 1457, 1331, 1258, 1137 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.14 (m, 4 H), 6.97–6.92 (m, 2 H), 6.82 (dd, *J* = 8.1, 1.1 Hz, 2 H), 3.38 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.9, 127.5, 127.3, 123.5, 122.6, 114.2, 35.4.

MS (EI+): *m*/*z* (%) = 198.1 (73), 213.1 (100, $[M]^+$).

HRMS (EI+): *m*/*z* $[M]^+$ calcd for $C_{13}H_{11}NS$: 213.0612; found: 213.0601.

9-Methyl-9*H*-carbazole (11-M)

Prepared from 9*H*-carbazole. Standard protocol workup after 24 h and purification by FCC [R_f = 0.3 (hexanes–EtOAc, 20:1)] gave the pure compound as a white solid; yield: 0.21 g (1.2 mmol, 61%). Starting from *N*-Boc-carbazole (**11**-Boc), the same solid product was obtained in slightly lower yield (0.17 g, 1.0 mmol, 49%); mp 84.4–85.3 °C; purity (HPLC): 97%; t_R = 3.9 min.

IR (KBr): 3433, 3049, 2926, 1598, 1467, 1323, 1246 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.0 Hz, 2 H), 7.45–7.40 (m, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.22–7.18 (m, 2 H), 3.70 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 141.1, 125.7, 122.8, 120.4, 118.9, 108.5, 29.0.

MS (EI+): *m*/*z* (%) = 152.1 (20), 166.1 (9), 181.1 (100, $[M]^+$).

HRMS (EI+): *m*/*z* $[M]^+$ calcd for $C_{13}H_{11}N$: 181.0891; found: 181.0884.

9-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (13-M)

Prepared from 2,3,4,9-tetrahydro-1*H*-carbazol-1-one. Standard protocol workup after 48 h and purification by FCC [R_f = 0.3 (hexanes–EtOAc, 10:1)] gave the pure compound as a yellow solid; yield: 0.11 g (0.6 mmol, 29%); mp 95.1–97.3 °C; purity (HPLC): 98%; t_R = 2.5 min.

IR (KBr): 3428, 2927, 2838, 1643, 1408, 1230, 935, 760 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.1 Hz, 1 H), 7.39–7.35 (m, 1 H), 7.30 (d, *J* = 8.5 Hz, 1 H), 7.14–7.10 (m, 1 H), 4.03 (s, 3 H), 2.97 (t, *J* = 6.1 Hz, 2 H), 2.63–2.59 (m, 2 H), 2.21–2.15 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.3, 139.7, 130.4, 129.2, 126.7, 124.7, 121.3, 120.0, 110.3, 40.1, 31.6, 24.8, 21.9.

MS (EI+): *m*/*z* (%) = 128.0 (20), 143.1 (63), 170.1 (40), 199.1 (100, $[M]^+$).

HRMS (EI+): *m*/*z* $[M]^+$ calcd for $C_{13}H_{13}NO$: 199.0997; found: 199.0988.

9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (14-M)

Prepared from 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole. Standard protocol workup after 48 h and purification by FCC [R_f = 0.3 (CH_2Cl_2 + 10% MeOH)] gave the pure compound as a yellow oil; yield: 0.24 g (1.3 mmol, 67%); purity (HPLC): 95%; t_R = 2.6 min.

IR (film): 3306, 3049, 2918, 2838, 1615, 1471, 1380, 1183, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dt, *J* = 7.8, 1.0 Hz, 1 H), 7.25 (dt, *J* = 8.2, 1.0 Hz, 1 H), 7.17 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.08 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1 H), 4.01 (t, *J* = 1.7 Hz, 2 H), 3.56 (s, 3 H), 3.15 (t, *J* = 5.7 Hz, 2 H), 2.79–2.72 (m, 2 H), 1.80 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.8, 134.4, 127.2, 121.0, 118.9, 117.9, 108.7, 107.7, 44.0, 42.5, 29.3, 22.7.

MS (EI+): *m*/*z* (%) = 142.1 (11), 157.1 (100), 186.1 (36, $[M]^+$).

HRMS (EI+): *m*/*z* $[M]^+$ calcd for $C_{12}H_{14}N_2$: 186.1157; found: 186.1152.

2-(1-Methyl-1*H*-indol-3-yl)ethan-1-amine (15-M)

Prepared from 2-(1*H*-indol-3-yl)ethan-1-amine (tryptamine). Standard protocol workup after 48 h and purification by FCC [R_f = 0.1 (CH_2Cl_2 + 10% MeOH)] gave the pure compound as a colorless oil; yield: 0.10 g (0.6 mmol, 30%); purity (HPLC): 96%; t_R = 3.0 min.

IR (film): 3347, 3050, 2926, 1578, 1473, 1328, 739 cm^{-1}.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.55 (d, *J* = 7.9 Hz, 1 H), 7.26 (d, *J* = 8.2 Hz, 1 H), 7.17 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.04 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1 H), 6.89 (s, 1 H), 3.69 (s, 3 H), 3.13 (s, 2 H), 2.97 (t, *J* = 6.8 Hz, 2 H), 2.89 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 137.6, 128.2, 127.5, 121.8, 119.1, 119.0, 111.9, 109.6, 42.4, 32.8, 28.5.

MS (ESI+): *m*/*z* (%) = 158.1 (100), 175.1 (78, $[M + H]^+$).

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{15}N_2$: 175.1230; found: 175.1231.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1381049.

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