Facile and efficient synthesis of thiosemicarbazone derivatives with functionalized pendant amines.

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Facile and Efficient Synthesis of Thiosemicarbazone Derivatives with Functionalized Pendant Amines.

By

Anna Elizabeth Davis

Submitted in partial fulfillment of the requirements for Graduation *summa cum laude*

and

for Graduation with Honors from the Department of Chemistry

University of Louisville

May, 2019
Facile and efficient synthesis of thiosemicarbazone derivatives with functionalized pendant amines

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Abstract

Bis-thiosemicarbazones are an important class of ligands for the synthesis of transition metal complexes with applications in medicine and electrochemistry.\(^{1,2}\) Among the most studied of these complexation ligands is diacetyl-2,3-bis(N\(^4\)-methyl-3-thiosemicarbazone) (denoted as ATSM, 1, Figure 1).\(^{2,3}\) Derivatives of 1 with various amines in place of the methylamine of ATSM have previously been reported, including diacetyl (N\(^4\)-methylthiosemicarbazone-N\(^4\)′-dimethylthiosemicarbazone) (denoted as ATSM/DM, 2).\(^{4}\) In this work, we pursue the development of a library of ATSM derivatives with a variety of functionalized pendant amines with a range of electronic and steric properties through the transamination of 2 with primary amines (molecules with an –NH\(_2\) group). The synthesis, yields, melting points, and \(^1\)H NMR spectra of a variety of new ATSM derivative ligands are reported.

Figure 1: ATSM (1) and ATSM/DM (2) Structures.

Keywords

thiosemicarbazone, transamination, ligands, amines
**Introduction**

Bis-thiosemicarbazones (BTSCs) are an important class of ligands for the synthesis of transition metal complexes with various applications. These include the treatment of cancer, tuberculosis, malaria, and stroke, as well as medical imaging agents for contrast in hypoxic cells.\(^1\,^2\) More recently, BTSC complexes have been evaluated as electrochemical catalysts for the hydrogen evolution reaction, which is the reduction of protons from acid and water to form hydrogen gas for fuel cells in an environmentally sustainable manner, as well as the activation of other small molecules.\(^3\) Among the most studied BTSCs is diacetyl-2,3-bis(N\(^{4}\)-methyl-3-thiosemicarbazone) (ATSM, 1, Figure 1).\(^2\) Deprotonation of 1 yields a dianionic N\(_2\)S\(_2\) chelate, a ligand that can complex with a metal atom, which possesses non-coordinating pendant amines that do not interact with the metal center. Numerous derivatives of 1 with variation of the pendant methylamine (--NHCH\(_3\) group) with other amines have previously been reported, including diacetyl-2,3-(N\(^{4}\)-methylthiosemicarbazone-N\(^{4}\)′-dimethylthiosemi-carbazone) (ATSM/DM, 2, Figure 1).\(^3\)

The general synthesis of 1 and its derivatives involves an elimination reaction between 2,3-butandione (top left of Scheme 1) and the appropriate thiosemicarbazide(s), many of which are commercially available.
Scheme 1: Synthesis of 1 and 2.\textsuperscript{2}

As shown on the top of Scheme 1, C\textsubscript{2\textnu}-symmetric BTSCs like 1 can be prepared in a single step. For C\textsubscript{s}-symmetric BTSCs like 2, a stepwise approach is required as shown on the left and bottom of Scheme 1. Using these approaches, a large number of BTSCs have been prepared.\textsuperscript{2} However, the routes are limited by the commercial or synthetic availability of the semicarbazide precursor. An alternate route to C\textsubscript{s}-symmetric BTSCs first reported by Buncic involves the transamination of 2, Figure 2\textsuperscript{3}. The “RNH\textsubscript{2}” abbreviates any primary amine; an R group denotes a variable part of the molecular structure, and the –NH\textsubscript{2} is the defining feature of a primary amine.

Figure 2: Transamination net reaction.\textsuperscript{3}

In this approach, the primary amine sulfanilic acid was used to displace the dimethylamine leaving group with a yield of 76%. The transamination method has also been successfully
employed by Xie, Lin, and Blower with good yields.\textsuperscript{1,5,6} The methodology of transamination in its simple one-step synthesis provides an advantage over labor-intensive thiosemicarbazide syntheses that can range from two to four steps.\textsuperscript{7-9}

To our knowledge, a systematic evaluation of the scope of the transamination reaction for the preparation of BSTCs and its tolerance to different R groups on the transaminated primary amine has not been reported. In this work, we report the scope of the transamination reaction of 2 through optimization of the synthetic strategy to include synthesis of new ATSM derivatives with primary amines containing functionalized substituents for further metal complexation ligand modifications. A variety of R groups on the primary amine were investigated, including both aliphatic (not containing an aromatic ring) and aromatic (containing an aromatic ring) amines, as well as the effect of reagent ratios, reaction solvent, and aromatic ring activation, a phenomenon in which the substituents of an aromatic ring affect its reactivity through inductive effects and/or resonance. The synthetic conditions, isolated yields (calculated by percentage: actual yield of the over theoretical yield of the pure product), and pure compound melting points are reported and summarized in Table 1. Isolated products were characterized by \textsuperscript{1}H NMR spectroscopy and melting point.
Methods

Materials and methods. All reagents were obtained from commercial sources and used as received unless otherwise noted. All solvents were purified with an MBraun solvent purification system prior to use. The BTSC compounds with derivative pendant amines were made according to modified literature methods.\(^1\) Specific details on conditions 1-4 (Table 1) are listed under Synthetic Methods. All reactions were performed under an inert atmosphere using standard Schlenk techniques.

Instrumental Methods. \(^1\)H NMR spectra were recorded on a Varian spectrometer at 500 MHz. Measurements were carried out in deuterated dimethyl sulfoxide (99.9% \(d_6\), Aldrich). Chemical shifts were calibrated relative to residual solvent peak (\(^1\)H NMR \(\delta_{\text{DMSO}} = 2.50\) ppm). Chemical shifts are reported in ppm (\(\delta\)), \(J\) values are given in Hz. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected.

Synthetic Methods. Condition 1 (See Table 1, entries 1, 3, 12, 14, 16, 18). A suspension of amine (1.50 mmol) and 2 (1.50 mmol) was made in 50 mL of acetonitrile. Hunig’s base (2.25 mmol) was added and the reaction mixture heated to reflux (81 °C) under an inert atmosphere for 24 hours. The resulting product was filtered hot and washed with diethyl ether. Isolated yield, melting point, and \(^1\)H NMR were taken to characterize the product.

Condition 2 (See Table 1, entries 2, 4-8, 10). A suspension of amine (3.00 mmol) and 2 (1.50 mmol) was made in 50 mL of acetonitrile. Hunig’s base (2.25 mmol) was added and the reaction mixture heated to reflux (81 °C) under an inert atmosphere for 24 hours. The resulting product was filtered hot and washed with diethyl ether. Isolated yield, melting point, and \(^1\)H NMR were taken to characterize the product.
**Condition 3** (See Table 1, entry 11). A suspension of amine (3.00 mmol) and 2 (1.50 mmol) was made in 50 mL of ethanol. Hunig’s base (2.25mmol) was added and the reaction mixture heated to reflux (78 °C) under an inert atmosphere for 24 hours. The resulting product was filtered hot and washed with diethyl ether. Isolated yield, melting point, and 1H NMR were taken to characterize the product.

**Condition 4** (See Table 1, entries 13, 15, 17, 19-22). A suspension of amine (3.00 mmol) and 2 (1.50 mmol) was made in 50 mL of tetrahydrofuran. Hunig’s base (2.25mmol) was added and the reaction mixture heated to reflux (66 °C) under an inert atmosphere for 24 hours. The resulting product was filtered hot and washed with diethyl ether. Isolated yield, melting point, and 1H NMR were taken to characterize the product.
Results

The transamination of 2 was investigated with a series of primary amines in order to develop the scope of the reaction. Isolated yields (reflecting the highest experimentally determined isolated yields) under a variety of reaction conditions for aliphatic and aromatic amines are provided in Table 1, as well as the melting points of the isolated products.

Table 1: Optimization of the synthesis of thiosemicarbazone derivatives from 2 and various primary amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Conditionsa</th>
<th>Isolated Yield (%)</th>
<th>Avg. Melting Point Range (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aliphatic Amines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Alanine</td>
<td>1</td>
<td>20</td>
<td>212.8 – 214.0</td>
</tr>
<tr>
<td>2</td>
<td>Alanine</td>
<td>2</td>
<td>85</td>
<td>212.8 – 214.0</td>
</tr>
<tr>
<td>3</td>
<td>Dimethyl ethylenediamine</td>
<td>1</td>
<td>14</td>
<td>213.4 – 215.1</td>
</tr>
<tr>
<td>4</td>
<td>Dimethyl ethylenediamine</td>
<td>2</td>
<td>87</td>
<td>213.4 – 215.1</td>
</tr>
<tr>
<td>5</td>
<td>Aminoethanethiol</td>
<td>2</td>
<td>98</td>
<td>213.6 – 214.3</td>
</tr>
<tr>
<td>6</td>
<td>Ethanolamine</td>
<td>2</td>
<td>98</td>
<td>234.1 – 234.4</td>
</tr>
<tr>
<td>7</td>
<td>Bromoethylamine HBr</td>
<td>2</td>
<td>77</td>
<td>211.0 – 211.9</td>
</tr>
<tr>
<td>8</td>
<td>Glycine</td>
<td>2</td>
<td>90</td>
<td>236.7 – 240.0</td>
</tr>
<tr>
<td>9</td>
<td>Glycine</td>
<td>4</td>
<td>40</td>
<td>236.7 – 240.0</td>
</tr>
<tr>
<td>10</td>
<td>Taurine</td>
<td>2</td>
<td>5</td>
<td>n/a</td>
</tr>
<tr>
<td>11</td>
<td>Taurine</td>
<td>3</td>
<td>20</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aromatic Amines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Para-aminobenzoic acid</td>
<td>2</td>
<td>72</td>
<td>196.6 – 197.3</td>
</tr>
<tr>
<td>13</td>
<td>Para-aminobenzoic acid</td>
<td>4</td>
<td>85</td>
<td>196.6 – 197.3</td>
</tr>
<tr>
<td>14</td>
<td>p-Aminophenol</td>
<td>2</td>
<td>62</td>
<td>231.2 – 232.7</td>
</tr>
<tr>
<td>15</td>
<td>p-Aminophenol</td>
<td>4</td>
<td>98</td>
<td>231.2 – 232.7</td>
</tr>
<tr>
<td>16</td>
<td>p-Isopropylaniline</td>
<td>2</td>
<td>32</td>
<td>214.5 – 221.1</td>
</tr>
<tr>
<td>17</td>
<td>p-Isopropylaniline</td>
<td>4</td>
<td>77</td>
<td>214.5 – 221.1</td>
</tr>
<tr>
<td>18</td>
<td>p-Aminobiphenyl</td>
<td>2</td>
<td>58</td>
<td>217.1 – 219.5</td>
</tr>
<tr>
<td>19</td>
<td>p-Aminobiphenyl</td>
<td>4</td>
<td>80</td>
<td>217.1 – 219.5</td>
</tr>
<tr>
<td>20</td>
<td>p-Anisidine</td>
<td>4</td>
<td>82</td>
<td>219.9 – 220.9</td>
</tr>
<tr>
<td>21</td>
<td>p-Fluroaniline</td>
<td>4</td>
<td>79</td>
<td>228.7 – 229.6</td>
</tr>
<tr>
<td>22</td>
<td>p-Nitroaniline</td>
<td>4</td>
<td>0</td>
<td>n/a</td>
</tr>
</tbody>
</table>

\( ^a \) Conditions: (1) Reflux 24h under \( N_2 \) in MeCN, 1:1 ratio of amine to 2. (2) Reflux 24h under \( N_2 \) in MeCN, 2:1 ratio of amine to 2. (3) Reflux 24h under \( N_2 \) in EtOH, 2:1 ratio of amine to 2. (4) Reflux 24h under \( N_2 \) in THF, 2:1 ratio of amine to 2.

Initial reactions were carried out in accordance with literature procedure\(^4\) with following modification: Hunig’s base (1.5 eq.) was added to the reaction mixture as a weak base in order to facilitate deprotonation of the proposed intermediate.\(^1\) All reactions were heated at reflux for 24 hours under an \( N_2 \) atmosphere. When a 1:1 ratio of alanine to 2 was employed under these conditions in acetonitrile, very poor isolated yield (20%, entry 1) was obtained. Increasing the
ratio of alanine to 2 to 2:1 improved the yield to 85% (entry 2). A similar increase in yield for the reaction with dimethyl ethylenediamine from 14% (entry 3) to 87% (entry 4) was obtained upon increasing the quantity of the amine. Under the same 2:1 conditions in acetonitrile, yields of 77 – 98% isolated yields were obtained for primary amines in the presence of various functional groups (entries 5 – 9) including –OH, -SH, -Br, -COOH. Notably, no product was isolated for reactions with taurine (entry 10) in acetonitrile. This is attributed to the zwitterionic nature of taurine, which is the presence of a negative and positive charge existing on the same molecule. On the taurine molecule, these disparate charges stem from the sulfonic acid group’s low pKa, necessitating it to exist as a negatively charged, deprotonated sulfonate group at the pH value of the transamination reaction conditions. The basic amine group also present on the molecule is protonated in turn and gains a positive charge. This phenomenon reduces the nucleophilicity and furthermore, the reactivity, of the amine group. The nitrogen atom’s lone pair of electrons is responsible for its ability to attack the electrophilic carbon of ATSM/DM, but cationic nitrogen atoms lack this lone pair since all valence electrons are involved in bonds. Modest yields, however, were obtained when the solvent was changed to ethanol (entry 11).

When aromatic amines were reacted using the conditions optimized for aliphatic amines, yields were poor to good (32 – 72%, entries 12 -15). It was hypothesized that this was a function of the relatively poor solubility of the aromatic amines in acetonitrile as compared with the smaller, more polar aliphatic amines. With solubility considered, tetrahydrofuran was selected as a reaction solvent for the aromatic amines due to its dielectric constant of 7.58, compared to 37.5 for acetonitrile. Using a 2:1 ratio of amine to substrate in THF, isolated yields improved to 77 – 98% (entries 16 – 19) for the aromatic amines tested previously. Similar yields were obtained for two additional aromatic amines (entries 20, 21). A notable exception to the success of transamination
with aromatic amines in THF was the strongly deactivated compound \( p \)-nitroaniline, which has a Hammett parameter of +0.778 and is not a strong enough nucleophile to attack the substrate. An aromatic molecule’s Hammett parameter is a quantified measurement of a ring substituent’s effect on the molecule’s reactivity.\(^\text{10}\) Attempts to obtain isolable product by increasing the amine to substrate ratio to 4:1 were unsuccessful.
Discussion

Scheme 2: Proposed transamination mechanism.\(^6\)

As demonstrated in Scheme 2, the proposed mechanism of transamination involves the nucleophilic attack of a slightly negative primary amine on the electrophilic (slightly positive) carbon of the thioketone alpha to the dimethyl amine functionalization of 2 (Step a). A charged tetrahedral intermediate is then formed (Step b). This leads to the reformation of the C=S of the thioketone (C=S group), causing the deprotonated dimethylamine anion (\(\text{N(CH}_3\text{)}_2^-\)) to leave (Step c). The dimethylamine anion then deprotonates the newly formed substituted secondary amine and leaves as a gas (Step d).

Scheme 3: Role of Hunig’s base in the mechanism.\(^1\)
Scheme 3 shows the mechanistic advantage of the addition of Hunig’s base at steps $b$ and $c$ of Scheme 2. The nitrogen cation (N$^+$) of intermediate $b$ is deprotonated by Hunig’s base in order to yield a more stable amine with far poorer leaving ability than the dimethylamine in intermediate $c_2$. Since the deprotonated amine has poor leaving group ability, it is less likely to break its newly formed bond than the dimethyl amine functionality. The dimethyl amine, more than ever, is comparatively more stable as an anion in solution with its two electron-donating methyl groups to stabilize its negative charge. This step leads to the immediate formation of BTSC product $d$ with only the dimethyl amine anion $e$ to be protonated by Hunig’s base and leave as a gas.

The transamination reaction of 2 with primary amines can be considered as an equilibrium process that is dependent on the basicity of the incoming amine relative to the amine leaving group (Figure 2). This postulate was the basis of our hypothesis upon embarking on this work. However, since the dimethylamine generated in the reaction leaves as a gas, the equilibrium of the reaction shifts towards the products, increasing the yield based on LeChatlier’s principle.$^{11}$ As such, reaction yields are not directly dependent on the thermodynamics of Figure 2, but rather by the ability of the primary amine and substrate to form the transition state preceding tetrahedral intermediate $b$ in Scheme 1. These effects suggest not a thermodynamic relationship between products and reactants, but a kinetic relationship. The 2:1 amine:substrate ratio was originally introduced in order to thermodynamically shift the equilibrium of the reaction toward the products, but upon realization that the dimethylamine leaves the reaction vessel, the equilibrium must be constantly shifted toward the product without modification of product concentrations. The expression for equilibrium constant can be seen in Figure 3, where $A = \text{ATSM/DM}$, $B = \text{RNH}_2$, $C = \text{ATSM/R}$, and $D = \text{NHMe}_2$, as shown in Figure 2.
Figure 3: Equilibrium constant expression. \(^{12}\)

\[
K_{eq} = \frac{[C]^c[D]^d}{[A]^a[B]^b}
\]

For equation \(aA + bB \rightarrow cC + dD\)

\[1 \text{ ATSM/DM} + 1 \text{ RNH}_2 \rightarrow 1 \text{ ATSM/R} + 1 \text{ (CH}_3\text{)_2NH}\]

Following Figure 3, A is denoted as ATSM/DM, B is denoted as RNH\(_2\) (the primary amine), C is denoted as the product ATSM/R, and D is the dimethyleamine byproduct. \(K_{eq}\) varies for every chemical reaction and the conditions in which it takes place. However, it is always a positive value. In such a case, if [D] (the concentration of dimethyleamine in the reaction vessel) approaches 0 if this reagent leaves as a gas, reagents A and B would be thermodynamically inclined to react to produce more ATSM/R to proceed toward the value of the equilibrium constant. Therefore, the advantage of a 2:1 ratio of amine to ATSM/DM lies not within the thermodynamics of the reaction, but in the kinetic rate law. A kinetic rate law defines how quickly a reaction proceeds based on the energy it takes to reach a transition state into a product or intermediate, in this case step \(b\) of Scheme 2. The rate law is variable per reaction, but depends on the concentration of the reagents in the reaction solution during the slowest (rate determining) step of the reaction. The strong improvement in isolated yields seen in the introduction of the 2:1 reagent ratio, then, is a function of the rate law of the reaction incorporating the concentration of the amine reagent on an order of one or more. The improvement of the solubility of the starting reagents in reaction solvent that also proved helpful in increasing yields reflects this hypothesis. If the reaction solution
better solvates the starting materials, their concentrations are higher, thus resulting in a faster rate of reaction over the 24 hour reflux period and a higher isolated yield.

As shown in Table 1, similar reaction yields are obtained for activated and deactivated aromatic amines. However, if the amine is strongly deactivated (entry 22) no isolable product is produced. The nucleophilicity of the deactivated amine is not strong enough to overcome the activation energy of the reaction, i.e. the energy of the transition state preceding the intermediate defined in Scheme 2 step b. If the reaction is not initiated, thermodynamic advantages of the dimethylamine gas leaving the reaction vessel become irrelevant.

Alternate solutions to the kinetic barriers for these syntheses have been explored, unsuccessfully. Aromatic amines are not tolerant to deprotonation by a strong or organometallic base in order to increase reactivity—bases strong enough to carry out a deprotonation have either destroyed the reagent or been unable to deprotonate the amine. Shifting the equilibrium and increasing the rate of the transamination by introducing a stronger excess of amine has not provided appreciably better yields in the 24 hour reflux period. The proposed modification of the dimethylamine functionalization to an O-alkyl or O-aryl functionalization proposed in the original hypothesis of this work is also rendered less relevant than originally expected by the kinetic control of the transamination reaction. The proposed O-methyl, O-ethyl, and O-phenyl groups, despite being more stable anions than NMe₂⁻ and therefore theoretically better leaving groups, are all liquids in their protonated forms. Since these byproducts would stay in the reaction vessel without special measures such as molecular sieves or a Dean Stark apparatus, their thermodynamic advantages fall outside of the research paradigm.
Conclusion

The scope of the transamination reaction of 2 with a variety of primary amines has been explored. Yields are reported for isolated products, which were characterized by \(^1\)H NMR spectroscopy and melting points. Reaction yields for aliphatic amines under optimized conditions (condition 2) are overall good (77%) to excellent (98%) for primary amines with a variety of other functional groups present. For aromatic amines, good (75%) to excellent (98%) yields were obtained in the presence of deactivating (–COOH and –F groups, entries 12 and 21) and stronger activating groups (entries 13, 15, 17, 19-21) under condition 4. However, aromatic amines with a very strongly deactivated ring (-NO\(_2\), entry 22) failed to yield isolable products after multiple attempts under current reaction conditions.

Future Directions

The novel ligands produced in the transamination reaction can potentially have wide applications in therapeutics and catalysis alike. This work provides a complete starting point for specific functionalization of TSCs in the aforementioned fields. It also offers a facile and efficient synthetic scheme for both proven and similar compounds for production in further research to replace the cumbersome syntheses of thiosemicarbazone precursors. Optimization of these yields, and furthermore, the transamination reaction itself, indeed brings about a simpler and less time- and reagent-expensive synthetic scheme for the preparation of bis-thiosemicarbazone derivative ligands.
Figure Legends

Figure 1: Molecular structures of ATSM (1) and ATSM/DM (2)

Scheme 1: Comparison between the synthetic routes of 1 and 2.

Figure 2: General reaction of 2 and a primary amine, RNH₂, to form a substituted BTSC derivative, ATSM/R. An R group denotes a part of the molecule that is variable in structure.

Table 1: Summary of transaminated amines onto 2, including optimization of synthetic conditions, isolated yields, and experimentally obtained melting points.

Scheme 2: Proposed stepwise mechanism of the transamination reaction unaided by Hunig’s base.

Scheme 3: Proposed mechanistic support provided by the addition of Hunig’s base to the reaction mixture.¹

Figure 3: Equilibrium constant expression, a fundamental thermodynamic equation.

¹H NMR spectra: Proton nuclear magnetic resonance spectroscopy (¹H NMR) is an analytical method used to elucidate or confirm the chemical structures of molecules. It is based on the magnetic moment generated by the dual quantum spin states of the proton nucleus. The NMR spectrometer applies a magnetic field to a molecular sample, then based on the magnetic resonances of the proton spins, applies a Fourier transform to the detected magnetic signal to generate a spectrum. The peaks in the spectra below are resonances of a proton or protons in identical chemical environments, i.e. on the same carbon. Based on the integration, splitting, and chemical shift (δ, in ppm) of the peaks, the structure of the analyte molecule can be confirmed. Below are ¹H NMR spectra of each transaminated compound, which serve as confirmation that they were successfully synthesized. Proton nuclei on the molecule are labeled alphabetically and assigned to their corresponding peak below the spectra. The x axis of these spectra, in ppm, is given from the difference between the frequency at which the proton spins resonate with the applied magnetic field and the resonance of an internal standard tetramethylsilane (TMS) in the same magnetic field, divided by the resonance of TMS. These units allow for consistency in chemical shift values across NMR instruments with different magnetic strengths through the use of TMS as an internal standard. The y axis is an arbitrary relative intensity value that allows for integration of the area under each peak to demonstrate the number of protons sharing that same resonance relative to the integration values of other peaks.
$^1$H NMR Spectra of Transaminated Compounds

ATSM/Alanine (entry 1)

$\delta$ (ppm) = 9.90 (v. br. s, 1H$_c$); 8.86 (br. s, 1H$_d$); 8.35 (br. s, 1H$_g$); 8.26 (d, $J = 4.0$ Hz, 1H$_b$); 3.34 (br. s, H$_2$O); 3.04 (d, $J = 4.0$ Hz, 3H$_a$); 3.03 (s, 3H$_i$); 2.50 (s, DMSO); 2.21 (s, 3H$_d$); 2.16 (s, 3H$_e$); 2.07 (s, MeCN); 1.35 (d, $J = 3.0$, 1H$_h$)
ATSM/Dimethyl ethylenediamine (entry 3)

\[ \delta (\text{ppm}) = 10.23 \text{ (br. s, 1H)}; 8.34 \text{ (br. s, 1H)}; 8.33 \text{ (br. s, 1H)}; 3.59 \text{ (q, } J = 7.5 \text{ Hz, 2H)}; 3.34 \text{ (s, H}_2\text{O)}; 3.00 \text{ (d, } J = 3.5 \text{ Hz, 3H)}; 3.03 \text{ (s, 3H)}; 2.50 \text{ (s, DMSO)}; 2.42 \text{ (t, } J = 7.5 \text{ Hz, 2H)}; 2.18 \text{ (s, 3H)}; 2.16 \text{ (s, 6H)}; 2.14 \text{ (s, 3H)}; 2.07 \text{ (s, MeCN)} \]
ATSM/Aminoethanethiol (entry 5)

\[
\begin{align*}
\delta (\text{ppm}) = 10.32 \text{ (br. s, } 1H_c); 10.23 \text{ (br. s, } 1H_d); 8.54 \text{ (t, } J = 5.5 \text{ Hz, } 1H_g); 8.38 \text{ (q, } J = 4.5 \text{ Hz, } 1H_i); 3.89 \text{ (br. s, } 1H_j); 3.70 \text{ (q, } J = 8.5 \text{ Hz, } 2H_h); 3.34 \text{ (s, } H_2O); 3.01 \text{ (d, } J = 4.5 \text{ Hz, } 3H_a); 2.70 \text{ (t, } J = 7.5 \text{ Hz, } 2H_n); 2.50 \text{ (p, DMSO); 2.21 (s, } 3H_o); 2.20 \text{ (s, } 3H_e); 2.07 \text{ (s, MeCN) }
\end{align*}
\]
ATSM/Ethanolamine (entry 6)

\[ \delta (\text{ppm}) = 10.28 \text{ (br. s, 1H}_a\text{); } 10.22 \text{ (br. s, 1H}_b\text{); } 8.35 \text{ (q, } J = 5.0 \text{ Hz, 1H}_b\text{); } 8.28 \text{ (t, } J = 5.0 \text{ Hz, } 1\text{H}_d\text{); } 7.93 \text{ (br. s, 1H}_c\text{); } 3.62 \text{ (q, } J = 7.0 \text{ Hz, 2H}_b\text{); } 3.40 \text{ (t, } J = 7.0 \text{ Hz, 2H}_i\text{); } 3.34 \text{ (s, H}_2\text{O); } 3.01 \text{ (d, } J = 4.5 \text{ Hz, 3H}_a\text{); } 2.87, 2.71 \text{ (m, Hunig’s Base); } 2.50 \text{ (p, DMSO); } 2.19 \text{ (s, 3H}_d\text{); } 2.16 \text{ (s, 3H}_e\text{)
ATSM/Bromoethylamine HBr (entry 7)

δ (ppm) = 10.07 (br. s, 1H_c); 8.24 (br. s, 1H_d); 8.35 (br. s, 1H_b); 7.97 (br. s, 1H_g); 7.65 (br. s, 1H_j); 3.57 (t, J = 9.0 Hz, 2H_i); 3.34 (s, H2O); 3.11 (t, J = 9.0 Hz, 2H_h); 3.01 (d, J = 4.5 Hz, 3H_a); 2.50 (p, DMSO); 2.10 (s, 6H_d,e)
$\delta$ (ppm) = 10.21 (br. s, 1H$_c$); 8.57 (q, $J$ = 4.5 Hz, H$_b$); 8.39 (t, $J$ = 5.5 Hz, 1H$_d$); 3.90 (d, $J$ = 4.0 Hz, 2H$_h$); 3.34 (s, H$_2$O); 3.02 (d, $J$ = 4.5 Hz, 3H$_a$); 2.50 (p, DMSO); 2.21 (s, 3H$_d$); 2.18 (s, 3H$_e$)
ATSM/Para-aminobenzoic acid (entry 12)

δ (ppm) = 12.59 (v. br. s, 1H); 10.71 (br. s, 1H); 10.27 (br. s, 1H); 10.09 (br. s, 1H); 8.37 (br. s, 1H); 7.89 (d, J = 10.0 Hz, 2H); 7.78 (d, J = 10.0 Hz, 2H); 3.34 (s, H₂O); 3.02 (d, J = 4.0 Hz, 3H); 2.50 (p, DMSO); 2.27 (s, 3H); 2.18 (s, 3H); 2.07 (s, MeCN)
ATSM/p-Aminophenol (entry 14)

δ (ppm) = 10.39 (br. s, 1Hc); 10.28 (br. s, 1Hi); 9.78 (s, 1Hg); 9.41 (s, 1Hb); 8.42 (br. s, 1Hj); 7.25 (d, \( J = 8.5 \) Hz, 2Hi); 6.75 (d, \( J = 8.5 \) Hz, 2Hb); 3.34 (s, \( H_2O \)); 3.04 (d, \( J = 4.5 \) Hz, 3Ha); 2.50 (p, DMSO); 2.28 (s, 3Hd); 2.25 (s, 3He)
ATSM/p-Iso propylaniline (entry 16)

δ (ppm) = 10.52 (br. s, 1Hc); 10.29 (br. s, 1Hd); 9.88 (s, 1He); 8.41 (s, 1Hf); 7.46 (d, J = 8.0 Hz, 2Hg); 7.24 (d, J = 8.0 Hz, 2Hh); 3.60 (t, THF); 3.34 (s, H2O); 3.04 (d, J = 4.5 Hz, 3Hi); 2.91 (m, J = 11.2 Hz, 1Hj); 2.50 (p, DMSO); 2.29 (s, 3Hk); 2.25 (s, 3Hl); 1.76 (p, THF); 1.22 (d, J = 11.2 Hz, 6Hm)
ATSM/p-Aminobiphenyl (entry 18)

\[ \delta \text{ (ppm)} = 10.64 \text{ (s, } 1\text{H}_c); \ 10.32 \text{ (s, } 1\text{H}_d); \ 10.01 \text{ (s, } 1\text{H}_b); \ 8.42 \text{ (s, } 1\text{H}_h); \ 7.68 \text{ (m, } J = 5.5 \text{ Hz, } 6\text{H}_i,j,k); \ 7.48 \text{ (t, } J = 6.0 \text{ Hz, } 2\text{H}_h); \ 7.34 \text{ (t, } J = 6.0 \text{ Hz, } 1\text{H}_i); \ 3.60 \text{ (t, THF); } 3.34 \text{ (s, H}_2\text{O); } 3.03 \text{ (d, } J = 4.0 \text{ Hz, } 3\text{H}_a); \ 2.50 \text{ (p, DMSO); } 2.31 \text{ (s, } 3\text{H}_d); \ 2.27 \text{ (s, } 3\text{H}_e) \]
ATSM/p-Anisidine (entry 20)

\[
\delta (\text{ppm}) = 10.47 (s, 1H_c); 10.27 (s, 1H_i); 9.84 (s, 1H_g); 8.41 (s, 1H_b); 7.49 (d, J = 6.0 Hz, 2H_i); 6.92 (d, J = 6.0 Hz, 2H_h); 3.76 (s, 3H_j); 3.34 (s, H_2O); 3.03 (d, J = 4.5 Hz, 3H_a); 2.50 (p, DMSO); 2.28 (s, 3H_d); 2.25 (s, 3H_e)
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ATSM/p-Fluoroaniline (entry 21)

δ (ppm) = 10.60 (s, 1H<sub>c</sub>); 10.28 (s, 1H<sub>i</sub>); 9.94 (s, 1H<sub>g</sub>); 8.41 (s, 1H<sub>b</sub>); 7.54 (dd, J = 5.0 Hz, 2H<sub>h</sub>); 7.20 (t, J = 9.0 Hz, 2H<sub>i</sub>); 3.60 (t, THF); 3.34 (s, H<sub>2</sub>O); 3.03 (d, J = 4.5 Hz, 3H<sub>a</sub>); 2.50 (p, DMSO); 2.29 (s, 3H<sub>d</sub>); 2.25 (s, 3H<sub>e</sub>)
References


