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A Simple Route to Unsymmetrically Substituted 1,2,4,5-Tetrazines

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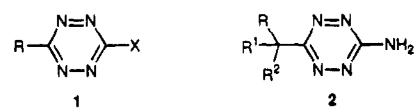
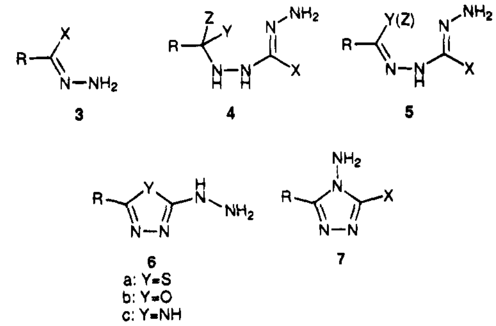
There is interest in the synthesis of 3,6-(disubstituted)-1,2,4,5-tetrazines **1** because they can be readily converted to triazines, pyridazines, and other heterocycles via a [4 + 2] cycloaddition with the appropriate dienophile followed by expulsion of molecular nitrogen (cycloreversion) and re-aromatization.[1] Our interest in tetrazines similarly stemmed from a desire to use them to access substituted pyridazines. We required a 6-*tert*-alkyl-3-amino-1,2,4,5-tetrazine (**2**) as our precursor. While there

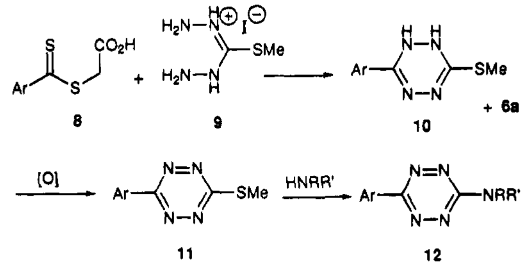


are many preparations of symmetrically substituted tetrazines,[2] few general preparations exist for unsymmetrically substituted (R ≠ X in **1**) tetrazines.[3–12] Of the preparations that exist, we could find no synthetically useful methods for preparing 6-alkyl-3-heteroatom substituted tetrazines when the alkyl substituent was tertiary. For example, the only reported preparations of 3-amino-6-*tert*-butyl-1,2,4,5-tetrazine **2a** (R = R^1 = R^2 = Me) gave 1%[6] and 3%[7] yields from readily available starting materials. We report herein a simple procedure for preparing multigram quantities of the title compounds, including **2a**, in 15–33% yield.

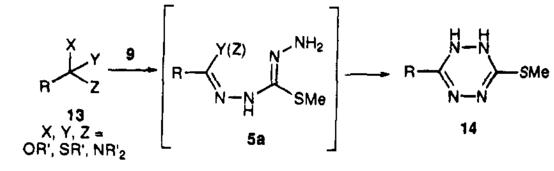
In most syntheses of 1,2,4,5-tetrazines described in the literature, ring formation proceeds through an intermediate such as **3**, **4**, and/or **5**. In such cases, when R is a sterically demanding substituent, the hydrazide carbon becomes less accessible and side reactions dominate. Specifically, when Y and/or Z is capable of nucleophilic attack (e.g. SH, OH, NHR), this atom initiates 5-membered ring formation to give **6**.[3,4] If X is sufficiently electron-donating, however, *N*-aminotriazoles **7** can result.[4]



Werbel and co-workers circumvented formation of **7** by employing *S*-methylisothiocarbonohydrazide salt **9** as a bis-aminoguanidine equivalent in the preparation of 6-aryl-3-aminotetrazines **12** from the dithiobenzoate esters **8** (eq 1).[3] In this case, the methylthio group served to deactivate the internal latent guanidine nitrogens for cyclization[4] as well as to provide a handle for subsequent amination.[8a]


(1)

However, significant quantities of thiadiazole **6a** were still produced from the alternative competitive cyclization of Y or Z = SH in the presumed intermediate **4a** or **5a** (X = SMe). For our studies, we surmised that reaction of a *tert*-alkyl dithiocarboxylic ester would promote even more formation of **6a** at the expense of formation of dihydrotetrazine owing to the increased steric encumbrance at the thiocarbonyl carbon. Thus, we sought to remove the potential for this competitive cyclization by starting with a carboxylic acid equivalent (**13**) such that *Y and Z* in an intermediate like **5a** is alkylated and cannot initiate deleterious cyclizations to give byproducts such as **6** (eq 2).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(1) For a review, see: Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. *Hetero Diels-Alder Methodology in Organic Synthesis*; Boger , D., Weinreb, S., Eds.; Academic Press, Inc.: New York, 1987.
(2) For example: (a) Cohen, V. I. *J. Heterocycl. Chem.* **1978**, *15*, 1113 and references cited therein. (b) Boger, D.; Coleman, R.; Panek, J. *J. Org. Chem.* **1985**, *50*, 5377.
(3) For an excellent overview of the varied approaches and side reactions in synthesis of 6-alkyl- or 6-aryl-3-(methylthio)-1,2,4,5-tetrazines, see: Werbel, L.; McNamara, J.; Colbry, N.; Johnson, J.; Degnan, M.; Whitney, B. *J. Heterocycl. Chem.* **1979**, *16*, 881 and references cited therein.
(4) Dithiolbenzoate esters **8** react with *S*-methylisothiocarbonohydrazide hydroiodide (**9**) to form dihydrotetrazines **10** followed by oxidation to (methylthio)tetrazines **11**: Esmail, R.; Kurzer, F. *J. Chem. Soc., Perkin Trans. I* **1975**, 1787.
(5) Takimoto, H. H.; Denault, G. C. *Tetrahedron Lett.* **1966**, 5369.
(6) Application of the Takimoto and Denault method[5] to the *tert*-butyl case found in ref 4 experimental.
(7) Counotte-Potman, A.; van der Plas, H. C. *J. Heterocycl. Chem.* **1981**, *18*, 123.
(8) 3-Aminotetrazines via amination of 3,6-bis(methylthio)-1,2,4,5-tetrazine: (a) Mangia, A.; Bortesi, F.; Amendola, U. *J. Heterocycl. Chem.* **1977**, *14*, 587. (b) Johnson, J.; Whitney, B.; Werbel, L. *J. Heterocycl. Chem.* **1980**, *17*, 501.
(9) 3-Alkyl-6-aryltetrazines: (a) Demus, D.; Krucke, B.; Kuschel, F.; Nothnick, H. U.; Pelzl, G.; Zaschke, H. *Mol. Cryst. Liq. Cryst.* **1980**, *56*, 115. (b) Lang, S. A.; Johnson, B. V.; Cohen, E. *J. Heterocycl. Chem.* **1975**, *12*, 1143.
(10) 6-Aryl-3-halotetrazines: Grakauskas, V.; Tomasewski, A.; Horwitz, J. *J. Am. Chem. Soc.* **1958**, *80*, 3155.
(11) 3,6-Diaryltetrazines: Brooker, P.; Parsons, J.; Reid, J.; West, P. *Pestic. Sci.* **1987**, *18*, 179.
(12) Imidate esters have been reacted with (a) formamidine acetate and hydrazine to give 3-aryltetrazines [Meresz, O.; Foster-Verner, P. A. *J. Chem. Soc., Chem. Commun.* **1972**, 951] and (b) with *S*-methylisothiocarbonohydrazide salts to give 6-aryl and secondary 6-alkyl-3-methylthiotetrazines [Just, M.; Thalmann, F. German (East) Patent, DD290011 A5910516; *Chem. Abstr.* **1982**, *115*, 185.
(13) Scott, E. S.; Audrieth, L. F. *J. Org. Chem.* **1954**, *19*, 1231.

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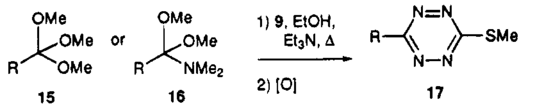
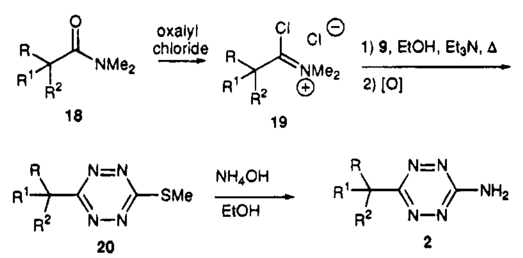
Preliminary success was obtained using triethyl orthoformate (**15a**), triethyl orthoacetate (**15b**) and dimethylformamide dimethyl acetal (**16a**). Oxidation was performed *in situ* by either bubbling air through the reaction vessel (only in the case of R = H) or by adding H_2O_2, Br_2, or $NaNO_2/CF_3CO_2H$. Column chromatography afforded a modest yield of tetrazines **17a,b**, whose bright red color is characteristic of this class of tetrazines (eq 3).



a: R=H; b: R=Me (3)

Unfortunately, more highly-substituted substrates such as pivalate orthoesters and amide acetals were difficult to prepare and reacted poorly with **9**, giving invariably low yields of 6-*tert*-butyl-3-(methylthio)tetrazine (**20a**).[14] However, utilization of the more reactive iminium chloride **19a** (Vilsmeier-type salt, formed by action of oxalyl chloride on *N,N*-dimethylpivalamide (**18a**) at rt in Et_2O for 5 min)[15] followed by *in situ* oxidation and amination with NH_4OH gave a 20–30% overall yield—the best yield reported to date—of 6-*tert*-butyl-3-amino-1,2,4,5-tetrazine (**2a**) (eq 4).



(4)

a: R=R¹=R²=Me; b: R=Me, R¹=R²=(CH₂)₂; c: R=H, R¹=R²=(CH₂)₅; d: R=n-Pr, R¹=R²=(CH₂)₅; e: R=Me, R¹=R²=Et; f: R=Me, R¹=R²=n-Pr g: R=Me, R¹=Et, R²=n-Bu

The desired hindered targets **2b–g** were prepared by analogy to the *tert*-butyl case above.[16] While *tert*-butyl, 1-methylcyclopropyl, and cyclohexyl *N,N*-dimethylamides **18a–c** reacted rapidly and cleanly with oxalyl chloride at rt, some of the more hindered amides did not. Iminium chloride formation was sluggish as the alkyl groups became excessively hindered, especially for **18e–g**. In such cases, 12 h in neat oxalyl chloride at 40 °C gave acceptable results; however, prolonged heating or elevated temperatures resulted in decomposition via alkyl group migration. An alternative milder activation method employs triphenoxyphosphorus dichloride, generated *in situ* at 0 °C in CH_2Cl_2.[17] Phosgene, thionyl chloride, phosphorus oxychloride, and phosphorus pentachloride gave poor results. Prereacting the iminium salt with ethanol gave poor results in our hindered cases.[18] In spite of the potential for reaction of ethanol with the iminium salt to give an imidate or amide acetal, however, alcoholic solvents still gave the best results.

Unlike in most previously reported syntheses of tetrazines, the intermediate dihydrotetrazines **14** do not need to be isolated. *In situ* oxidation was best achieved using biphasic $NaNO_2$/aqueous HOAc/hexane. These conditions seemed to be more selective for oxidizing dihydrotetrazine to tetrazine without oxidizing the tetrazine methylthio group or any of the hydrazino intermediates.

In conclusion, we have developed a new, two step, one pot procedure for preparing unsymmetrically substituted 6-alkyl-3-(methylthio)-1,2,4,5-tetrazines. This method supplements existing methodology in being able to access tetrazines bearing tertiary alkyl groups and is amenable to scale-up. These compounds are readily converted to 6-alkyl-3-aminotetrazines **2** by published procedures (NH_4OH/EtOH at rt) in 70–90% yield.[8a] A manuscript detailing the conversion of these compounds to other heterocycles via [4 + 2] cycloaddition is in preparation.

Experimental Section

General. All solvents and reagents were of reagent grade or higher. All reagents were purchased from Aldrich unless otherwise indicated. *S*-Methylisothiocarbohydrazide hydroiodide (**9**) was prepared according to the cited literature.[12b,13] Amides **18b**,[19] **18c**,[20] **18d**,[21] and **18e**[22] were prepared according to the cited literature or by analogy to the preparation of **24b**. TLC and medium pressure liquid chromatography (MPLC) employed silica gel 60, and 270 MHz ^1H NMR, 100 MHz ^{13}C NMR, and IR were recorded in $CDCl_3$ unless noted.

Preparation of 3-(Methylthio)-1,2,4,5-tetrazine (17a) from an Amide Acetal. *N,N*-Dimethylformamide dimethyl acetal (**15a**) (94%; 7.9 mmol, 1.11 mL) was added rapidly to **9** (7.5 mmol, 1.86 g) suspended in absolute EtOH (50 mL) at *ca.* 50 °C. The suspension became a yellow homogeneous solution over 5 min, at which time Et_3N (7.5 mmol, 1.04 mL) was added. The solution turned to faint pink. After 30 min of reflux, the red-orange solution was oxidized by adding $NaNO_2$ (97%; 15 mmol, 1.07 g) followed by CF_3CO_2H (7.5 mmol, 0.58 mL) and heated an additional 30 min, during which time the solution turned deep red. Hexane (50 mL) was added, and the nitrous fumes were chased with an active air purge for 30 min as the solution cooled to rt. The solution was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed twice with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to a red oil.

The product **17a** was isolated by plug filtration (silica gel, 5% Et_2O/hexane) to give 340 mg of a red solid (35% yield). Note: the product is *extremely volatile* and is difficult to obtain solvent free, especially if less volatile solvents are used. Physical analysis of the material was consistent with that given in the literature for **17a**:[8a] TLC R_f = 0.45, 1:5 EtOAc/hexane.

Preparation of 3-(Methylthio)-6-methyl-1,2,4,5-tetrazine (17b) from an Orthoester. The procedure above was used with triethyl orthoacetate (**15b**) (97%; 8.25 mmol, 1.55 mL) to give 425 mg (40% yield) of **17b** as a red oil. Note: the product is *extremely volatile*. **17b**: TLC R_f = 0.40, 1:5 EtOAc/hexane; MS (EI, *m/z*) 143 (M + 1); IR 1432, 1306 cm^{-1}; 300 MHz ^1H NMR δ 2.87 (3 H, s), 2.61 (3 H, s); ^{13}C NMR δ 175.1, 165.0, 20.6,

(14) The method of Just and Thalmann (ref 12b) similarly failed because pivaloyl nitrile is too hindered to react under their reaction conditions to form the prerequisite imidate ester.

(15) Fujisawa, T.; Mori, T.; Sato, T. *Tetrahedron Lett.* **1982**, *23*, 5059.

(16) The desired *N,N*-dimethylamides **18b–g** were prepared by Schotten–Baumann acylation in 70–90% yield.[23] To achieve the desired *tert*-alkyl substitution, alkylation of secondary amides was the method of choice for the acyclic series. However, this method failed for preparation of *N,N*-dimethylcyclohexanecarboxamide (**18c**), giving primarily O-alkylation rather than the desired tertiary amide **18d**. Traditional alkylation of the ester enolate followed by saponification and amination of the resulting *tert*-alkyl carboxylic acid was used to prepare amide **18d**. The rest of the amides could also be prepared in this way, or by literature procedures.[19–22]

(17) Rydon, H. N.; Tonge, B. L. *J. Chem. Soc.* **1956**, 3043.

(18) Formamidine acetate and imidates have been shown to react under these conditions to give tetrazines in unhindered cases.[2,9,12]

(19) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1980**, *59*, 49.

(20) Hobbs, C. F.; Weingarten, H. *J. Org. Chem.* **1974**, *39*, 918.

(21) Rowsell, D. G.; Gascoyne, J. M.; Hems, R. (Wilkinson Sword Ltd., UK). United States Patent US 4296093 A; Oct 20, 1981; Chem. Abstr. **1982**, *96*, 68444k.

(22) Mulet Pons, A.; Berna Prats, A.; Aucejo Perez, A. *Ing. Quim. (Madrid)* **1978**, *10*, 113.

13.2. Anal. Calcd for $C_4H_6N_4S$ (142.18): C, 33.79; H, 4.25. Found: C, 33.92; H, 4.50.

Preparation of *N,N*,2-Trimethylpentanamide. Schotten–Baumann acylation[23] was used to convert 2-methylpentanoic acid (1.0 mol, 116 g) to 130 g of a yellow oil which was distilled (65–70 °C/2 mmHg) to give 116 g of pure amide (81% yield). The product has a characteristic unpleasant odor and is a lachrymator: MS (EI, *m/z*) 144 (M^+, 90), 72 (100); IR 2963, 2875, 1650 cm^{-1}; ^1H NMR δ 2.99 (3 H, s), 2.88 (3 H, s), 2.68–2.62 (1 H, m), 1.60–1.55 (1 H, m), 1.30–1.19 (3 H, m), 1.01 (3 H, d, J = 4.6 Hz), 0.82 (3 H, t, J = 4.7 Hz); ^{13}C NMR δ 176.5, 36.9, 36.2, 35.3, 35.1, 20.3, 17.1, 13.7. Anal. Calcd for $C_8H_{17}NO$ (143.73): C, 67.09; H, 11.96; N, 9.78. Found: C, 67.19; H, 11.65; N, 9.85.

Tertiary Amides via Amide Enolate Alkylation: Preparation of 2-Propyl-*N,N*,2-trimethylpentanamide (18f). To LDA (2.0 M in heptane/THF/ethylbenzene; 0.56 mol, 280 mL) in of dry THF (500 mL) at rt under N_2 was added the *N,N*,2-trimethylpentanamide from above (0.37 mol, 53.3 g) in dry THF (50 mL) dropwise over 30 min. Iodopropane (99%; 0.56 mol, 55.3 mL) was added dropwise over 15 min after an additional 30 min of stirring. The reaction exothermed to *ca.* 45 °C. The solution was stirred for 12 h as it cooled to rt. The volatiles were removed, and the resultant brown oil was dissolved in Et_2O (400 mL) and partitioned with N NaOH (400 mL). The aqueous phase was extracted with Et_2O (3 × 75 mL), and the combined extracts were dried ($MgSO_4$) and concentrated to give 59 g of a yellow oil which was distilled (bp 54–57 °C/0.4 mmHg) to give 54 g of product **18f** (80% yield). ^1H NMR revealed a >20:1 ratio of product to starting material. **18f:** MS (EI, *m/z*) 186 (M + 1, 95), 72 (100); IR 2935, 2860, 1635 cm^{-1}; ^1H NMR δ 3.01 (6 H, s), 1.71 (2 H, m), 1.42 (2 H, m), 1.32 (4 H, m), 1.13 (3 H, s), 1.05–0.84 (3 H, m), 0.80 (3 H, m); ^{13}C NMR δ 176.1, 46.8, 42.2, 38.0, 24.8, 18.0, 14.7.

18g. Starting with 2-methylbutyric acid (0.5 mol), using the amination and alkylation methods above with bromobutane instead of iodopropane, 49.2 g of product **18g** were isolated (53% yield over two steps). Pure material was obtained as a colorless liquid by distillation (75–80 °C/1.5 mmHg). **18g:** MS (EI, *m/z*) 186 (M + 1, 95), 72 (100); IR 2960, 2875, 1637 cm^{-1}; ^1H NMR δ 2.97 (6 H, s), 1.95–1.75 (2 H, m), 1.60–1.15 (5 H, m), 1.13 (3 H, s), 1.05 (1 H, m), 0.82 (3 H, t, J = 8.5 Hz), 0.78 (3 H, t, J = 8.5 Hz); ^{13}C NMR δ 176.1, 47.1, 39.2, 38.0, 32.1, 26.9, 24.2, 23.4, 14.0, 9.1.

Iminium Chloride Formation. Method A. Oxalyl chloride (206 mmol, 18.0 mL) was added to *N,N*-dimethylcyclohexanecarboxamide (**18c**) (187 mmol, 29.0 g) in dry Et_2O (500 mL) at rt. Gas evolved vigorously for 5 min during which time a precipitate formed. The precipitate was separated quickly by vacuum filtration, washed with dry Et_2O, and dried on a vacuum pump for 1 h (20 °C/0.1 mmHg) to give 35 g (90% crude yield) of hygroscopic white solid **19c** which was used without further purification.

Iminium Chloride Formation. Method B. Oxalyl chloride (*ca.* 10 equiv, 2.2 mol, 190 mL) was added to *N,N*-dimethyl-3-methylheptane-3-carboxamide (**18g**) (216 mmol, 40 g), and the solution was stirred under N_2 at 40 °C for 12 h during which time gas expulsion slowly occurred. The excess oxalyl chloride and HCl were removed (rotary evaporator, then high vacuum for 1 h). The resultant homogeneous brown, hygroscopic, noxious oil **19g** was used without further purification.

Iminium Chloride Formation. Method C. Chlorine gas (CMS; 21 mmol, 1.5 g) was slowly bubbled into solution of *N,N*-dimethylpivalamide (**18a**) (Pfaltz and Bauer; 20 mmol, 2.58 g) and triphenyl phosphite (20 mmol, 6.2 g) in CH_2Cl_2 (40 mL) at 4 °C. The mixture was stirred for 12 h while being warmed to rt. Solvent was removed *in vacuo* , affording an off-white semisolid **19a**. For higher chain amides, the product mixtures were usually clear, viscous oils which were used without further purification.

Dihydrotetrazine Formation: Preparation of 3-(Methylthio)-6-*tert*-butyl-1,2,4,5-dihydrotetrazine. Iminium salt **19a** (208 mmol, 43 g) was added portionwise over 5 min to **9** (229 mmol, 55 g), excess Et_3N (625 mmol, 86.5 mL), and absolute EtOH (800 mL) in a 2 L Erlenmeyer flask under a blanket of N_2 with an active purge. A slight exotherm was noticeable, as was fuming (presumably from HCl production). Stirring continued for 30 min after addition was complete; then the solution was heated to reflux for 15 min during which time it became homogeneous and red-orange in color. Some tetrazine was apparent at this stage by TLC, but the majority required *in situ* oxidation by one of the two methods listed below.

(23) Ugi. *J. Chem. Res., Synop.* **1982**, 271.

Table 1. Preparation of Tetrazines from *N,N*-Dimethylamides

entry	compd	alkyl group	activated[a]	oxidation[b]	% yield
1	**20a**	*tert*-butyl	A	D	20–25
2	**20a**	*tert*-butyl	C	E	37
3	**20a**	*tert*-butyl	A	E	19
4	**20b**	methylcyclopropyl	A	D	28
5	**20c**	cyclohexyl	A	D	33
6	**20d**	propylcyclohexyl	B	D	15
7	**20e**	3-methylpentyl	B	E	15–20
8	**20f**	4-methylheptyl	B	E	17–22
9	**20f**	4-methylheptyl	C	E	23
10	**20g**	3-methylheptyl	B	D	19
11	**20g**	3-methylheptyl	B	E	33

[a] A, oxalyl chloride, rt; B, oxalyl chloride, 40 °C; C, triphenoxyphosphorus dichloride, 4–5 °C. [b] D, Br_2; E, $NaNO_2$/glacial HOAc.

***In situ* Oxidation. Method D: Preparation of 3-(Methylthio)-6-*tert*-butyl-1,2,4,5-tetrazine (20a) via Br_2 Oxidation.** After reaction to form dihydrotetrazine **19a** was performed on a 208 mmol scale, air was vigorously bubbled through the solution and Br_2 (208 mmol, 10.7 mL) was added portionwise over 10 min. The solution fumed and turned dark immediately. The mixture was refluxed 30 min with air vigorously bubbling through it to chase residual Br_2 vapors.

To the cooled solution was added 1 N HCl (100 mL), and the aqueous portion was extracted (4 × 1 L of 20% EtOAc/hexane) and the combined organic layers were concentrated to a dark red oil. Polar material was removed by plug filtration on silica gel (5% EtOAc/hexane) and then purified via MPLC to give 7.5 g (20% yield) of **20a** (Table 1).

***In Situ* Oxidation. Method E: Preparation of 3-(Methylthio)-6-*tert*-butyl-1,2,4,5-tetrazine (20a) via $NaNO_2$/Aqueous Glacial HOAc Oxidation.** After reaction to form dihydrotetrazine **19a** was performed on a 100 mmol scale, $NaNO_2$ (97%; 200 mmol, 1.38 g) was added via spatula followed by 100 mL of glacial HOAc, 200 mL of H_2O, and finally 300 mL of hexane. The biphasic solution began to turn dark immediately as it was vigorously stirred. The mixture was heated to reflux for 30 min and purged with a N_2 line to chase nitrous vapors.

The cooled solution was extracted (4 × 1 L of hexane), and the combined organic layers were concentrated (without drying) to *ca.*10 g of a dark red oil, which was purified via column chromatography (5% EtOAc/hexane) to give 5.0 g (27% yield) of **20a**.

20a. Pure material was obtained by MPLC (1:9 EtOAc/hexane) followed by recrystallization (hexane) to afford magenta crystals: mp 60–61 °C; TLC R_f = 0.85, 1:4 EtOAc/hexane; MS (EI, *m/z*) 184 (M^+, 30), 73 (100); IR 2873, 1487, 1310, 1200 cm^{-1}; UV (EtOH, nm) λ (ϵ) 542 (400), 366 (808), 260, (16253); ^1H NMR δ 2.76 (3 H, s), 1.55 (9 H, s); ^{13}C NMR δ 174.8, 173.5, 37.5, 29.1, 17.5. Anal. Calcd for $C_7H_{12}N_4S$ (184.26): C, 45.63; H, 6.56; N, 30.41. Found: C, 45.40; H, 6.46; N, 30.20.

20b. Starting with 100 mmol of *N,N*-dimethylamide **18b** and using iminium chloride forming method A and oxidation method D, 5.5 g of product was isolated (30% yield). Pure material was obtained by MPLC (1:9 EtOAc/hexane) as a deep red oil: TLC R_f = 0.68, 1:4 EtOAc/hexane; MS (EI, *m/z*) 182 (M^+, 80), 73 (100); IR 2850, 1469, 1373, 1219 cm^{-1}; ^1H NMR δ 2.74 (3 H, s), 1.71 (3 H, s), 1.65–1.55 (2 H, m), 1.20–1.12 (2 H, m); ^{13}C NMR δ 174.0, 170.8, 20.3, 19.8, 19.0, 13.3. Anal. Calcd for $C_7H_{10}N_4S$ (182.25): C, 46.13; H, 5.53; N, 30.74. Found: C, 46.32; H, 5.75; N, 30.49.

20c. Starting with 187 mmol of *N,N*-dimethylamide **18c** using iminium chloride forming method A and oxidation method D, 12.6 g of product was isolated (32% yield). Pure material was obtained by MPLC (1:9 EtOAc/hexane) as a red oil: TLC R_f = 0.65, 1:4 EtOAc/hexane; MS (EI, *m/z*) 210 (M^+, 90), 73 (100); IR 2854, 1726, 1190 cm^{-1}; ^1H NMR δ 3.35–3.15 (1H, m), 2.76 (3 H, s), 2.2−1.2 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 175.6, 170.7, 43.1, 31.4, 25.9, 25.6, 13.2.

20d. Starting with 93 mmol of *N,N*-dimethylamide **18d** using iminium chloride forming method B and oxidation method D, 3.5 g of product was isolated (15% yield). Pure material was obtained by MPLC (1:9 EtOAc/hexane) as a red viscous oil: TLC R_f = 0.66, 1:5 EtOAc/hexane; MS (EI, *m/z*) 252 (M^+, 100), 73 (100); IR 2854, 1450, 1248 cm^{-1}; ^1H NMR δ 2.81 (3 H, s), 2.6−2.5 (2 H, br m), 1.90−1.20 (10 H, m), 1.15−0.98 (2 H, m), 0.83 (3 H, t, J = 6.9 Hz); ^{13}C NMR δ 174.3, 172.0, 45.1, 35.9, 34.7, 26.1, 23.1, 22.7, 16.9, 14.4, 13.1. Anal. Calcd for $C_{12}H_{20}N_4S$ (252.38): C, 57.11; H, 7.99; N, 22.20; S, 12.70. Found: C, 57.17; H, 8.09; N, 22.07; S, 12.80.

20e. Starting with 95 mmol of *N,N*-dimethylamide **18e** using iminium chloride forming method B and oxidation method E, 3.0 g of product was isolated (15% yield). Pure material was obtained by MPLC (1:5 EtOAc/heptanes) as a red viscous oil: TLC R_f = 0.39, 1:4 EtOAc/heptanes; MS (EI, *m/z*) 212 (M^+, 100); IR (CH_2Cl_2) 2882, 1462, 1306 cm^{-1}; 300 MHz ^1H NMR (DMSO) δ 2.76 (3 H, s), 2.10−1.90 (2 H, m), 1.90−1.70 (2 H, m), 1.40 (3 H, s), 0.71 (6 H, t, J = 6.9 Hz); ^{13}C NMR (DMSO) δ 174.2, 171.3, 43.8, 32.3, 21.3, 12.7, 8.3. Anal. Calcd for $C_9H_{16}N_4S$ (212.32): C, 50.91; H, 7.60; N, 26.39. Found: C, 51.13; H, 7.64; N, 26.45.

20f. Starting with 50 mmol of *N,N*-dimethylamide **18f** using iminium chloride forming method B and oxidation method E, 2.5 g of product was isolated (22% yield). Pure material was obtained by MPLC (5% EtOAc/hexane) as a magenta oil: TLC R_f = 0.65, 1:4 EtOAc/hexane; MS (EI, *m/z*) 240 (M^+, 100); IR 2850, 1467, 1250 cm^{-1}; 300 MHz ^1H NMR δ 2.72 (3 H, s), 2.05−1.90 (2 H, m), 1.80−1.65 (2 H, m), 1.49 (3 H, s), 1.35−1.10 (2 H, m), 1.05−0.85 (2 H, m), 0.82 (6 H, t, J = 7.0 Hz); ^{13}C NMR δ 174.5, 172.5, 44.1, 43.3, 22.6, 17.6, 14.6, 13.3. Anal. Calcd for $C_{11}H_{20}N_4S$ (240): C, 54.96; H, 8.39; N, 23.32. Found: C, 54.57; H, 8.49; N, 22.93.

20g. Starting with 46 mmol of *N,N*-dimethylamide **18g** using iminium chloride forming method B and oxidation method D, 2.1 g of product was isolated (19% yield). Pure material was obtained by MPLC (1:9 EtOAc/hexane) as a red viscous oil: TLC R_f = 0.90, 1:2 EtOAc/hexane; MS (EI, *m/z*) 240 (M^+, 100), 73 (100); IR 2861, 1464, 1284 cm^{-1}; ^1H NMR δ 2.78 (3 H, s), 2.20−1.99 (2H, m), 1.95−1.73 (2H, m), 1.53 (9 H, s), 1.4−0.8 (4 H, m), 0.90 (3 H, t, J = 6.9 Hz), 0.79 (3 H, t, J = 7.0 Hz); ^{13}C NMR δ 174.6, 172.5, 44.3, 40.3, 33.4, 26.6, 23.3, 22.1, 13.9, 13.2, 8.7. Anal. Calcd for $C_{11}H_{20}N_4S$ (240): C, 54.96; H, 8.39; N, 23.31. Found: C, 54.89; H, 8.39; N, 23.31.

Preparation of 3-(Methylthio)-6-(3-(3-methylheptyl))-1,2,4,5-tetrazine (20g) on a Semipreparative Scale. Three 2 L flasks were charged with absolute EtOH (1 L), **9** (130 mmol, 31.2 g), and Et_3N (325 mmol, 45 mL) according to the dihydrotetrazine formation method. After 15 min, the iminium salt **19g** (prepared from 120 g of *N,N*-dimethyl-3-methylheptane-3-carboxamide (**18g**) and 570 mL of oxalyl chloride according to the iminium chlorideforming method B) was dissolved in 20 mL of CH_2Cl_2 and added portionwise via pipette to the vigorously stirred solution over 5 min and stirred an additional 30 min. Each mixture was oxidized according to oxidation method E by adding $NaNO_2$ (97%; 440 mmol, 30 g) via spatula followed by glacial HOAc (100 mL), H_2O (200 mL), and finally hexane (300 mL). Column chromatography (silica gel) after workup gave a combined 50 g (32% yield) of **20g**.

Amination of a Hindered (Methylthio)tetrazine: Preparation of 3-Amino-6-(3-(3-methylheptyl))-1,2,4,5-tetrazine (2g). (Methylthio)tetrazine **20g** from above (208 mmol, 50 g) was treated with NH_4OH (400 mL) and 95% EtOH (600 mL) for 12 h at 35 °C. After 12 h, the solution was diluted with H_2O (5 L), exhaustively extracted with EtOAc (minimum 5 × 2 L), and dried ($MgSO_4$), and concentration gave a dark red oil which was purified by plug filtration (silica gel, 2:1 hexane/EtOAc) to give 30.1 g of **2g** (90% yield). Pure material was obtained by MPLC (1:4 EtOAc/hexane) followed by recrystallization from hexane to afford red crystals **2g**: mp 73.5 °C; TLC R_f = 0.50, 1:2 EtOAc/hexane; MS (EI, *m/z*) 209 (M^+, 80), 68 (100); IR 3316 (br), 3191 (br), 2857, 1647, 1523 cm^{-1}; ^1H NMR δ 3.78 (3 H, s), 2.20−1.99 (2H, m), 1.95−1.73 (2H, m), 1.53 (9 H, s), 1.4−0.8 (4H, m), 0.90 (3H, t, J = 6.9 Hz), 0.79 (3H, t, J = 7.0 Hz); ^{13}C NMR δ 170.8, 162.5, 43.7, 40.4, 33.5, 26.6, 23.3, 22.3, 14.0, 8.7. Anal. Calcd for $C_{10}H_{19}N_5$ (209): C, 57.38; H, 9.15; N, 33.47. Found: C, 57.42; H, 8.92; N, 33.54.

2a. (Methylthio)tetrazine **20a** (41 mmol) was aminated as for **2g** to give after MPLC (1:2 EtOAc/hexane) and recrystallization (hexane) 5.5 g (88% yield) of **2a** as red needles: mp 113−115 °C; TLC R_f = 0.50, 1:2 EtOAc/hexane; MS (EI, *m/z*) 153 (M^+, 15), 57 (100); IR 3310 br, 3202 br, 1640, 1523, 1175 cm^{-1}; UV (EtOH, nm) λ (ϵ) 534 (532), 359 (2012), 233 (14 935); ^1H NMR δ 5.90−5.60 (1 H, br s), 1.53 (9 H, s); ^{13}C NMR δ 171.7, 162.4, 37.1, 29.3. Anal. Calcd for $C_6H_{11}N_5$ (153.19): C, 47.04; H, 7.24; N, 45.72. Found: C, 46.45; H, 7.10; N, 46.48.

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Supplementary Material Available: Copies of ^1H and ^{13}C spectra for all compounds (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.