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Microwave-Assisted Synthesis of Tri-Substituted 1,3,5-Triazines from Metformin Using Benzotriazole Chemistry

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Abstract: A simple, metal-free, cost-effective, and eco-friendly protocol for the preparation of trisubstituted 1,3,5 triazine from metformin using benzotriazole chemistry is reported. Short reaction time, large-scale synthesis, easy and quick isolation of the product, and excellent yield are the main advantages of this procedure. Furthermore, the use of benzotriazole chemistry results in a product free from metal traces. Our optimized reaction condition and methodology overcome the challenges of using a metal catalyst, such as a longer reaction time, lower yields, and expensive starting materials.

Keywords: metformin; 1,3,5-triazine; benzotriazole; synthesis; microwave

1. Introduction

Metformin (**4**) belongs to the biguanide class of compounds and is used as the first-line medication for type II diabetes [1]. It initially entered the spotlight as a promising anticancer agent due to epidemiologic reports that it reduced cancer risk and improved clinical outcomes in diabetic patients taking metformin [2]. To uncover the anticancer mechanisms of metformin, preclinical studies determined that metformin impairs cellular metabolism and suppresses oncogenic signaling pathways. Recently, the anticancer potential of metformin has gained increasing interest due to its inhibitory effects on cancer stem cells (CSCs), which are associated with tumor metastasis, drug resistance, and relapse [3,4]. This drug needs to be optimized to target a more general audience, non-diabetic cancer patients. Metformin has low bioavailability, a narrow absorption window, and extensive liver metabolism. Its oral administration is accompanied by gastrointestinal adverse effects, including nausea, abdominal pain, abdominal bloating, flatulence, dyspepsia, and anorexia, resulting in up to 50% of patients [5]. In addition to this, metformin is used as a key synthetic scaffold to synthesize biologically important triazines.

Heterocycles play an immensely important role in the development of pharmaceutical agents. Several approaches have been investigated and developed for the synthesis of heterocyclic systems [6–11]. Triazines hold a prominent position among all the nitrogen-containing heterocyclics and are known for various pharmacological properties, such as antibacterial, anticancer, anti-HSV-1, antimalarial composition, and anti-HIV activities [12–16]. Several 1,3,5-triazine-based agents have been used for the treatment of various types of cancer (Figure 1). Traditionally, trisubstituted 1,3,5-triazine derivatives are synthesized by cyanuric chloride nucleophilic substitution reactions [17]. With advancements in the field of chemistry, several reactions of substituted biguanides with anhydrides, acid chlorides, and carboxylates or by cyclization of acyl amidines with amidines or guanidine catalyzed by organometallic reagents, have been reported [18–20]. Ming Zeng reported ruthenium-catalyzed synthesis of tri-substituted 1,3,5-triazines from alcohols and biguanides under mild conditions [21,22]. Similarly, Chen Zhang et al. reported a synthesis of substituted 2,4-diamino-1,3,5-triazanes from 1,1-dibromoalkenes and biguanides using CuI as a catalyst and 2,2′ bipyridine as a ligand [23]. Recently, Chaurasia et al. reported a metal-free graphene oxide-based carbon catalyst for the synthesis of tri-substituted 1,3,5-triazines [24].

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Although the reported methods provide a good yield of product, the use of an organometallic catalyst, such as iridium, and ruthenium for the synthesis encounters some concerns, such as the use of costly catalysts, catalyst separation, bioaccumulation, selectivity, and longer reaction time, etc. [25–27].

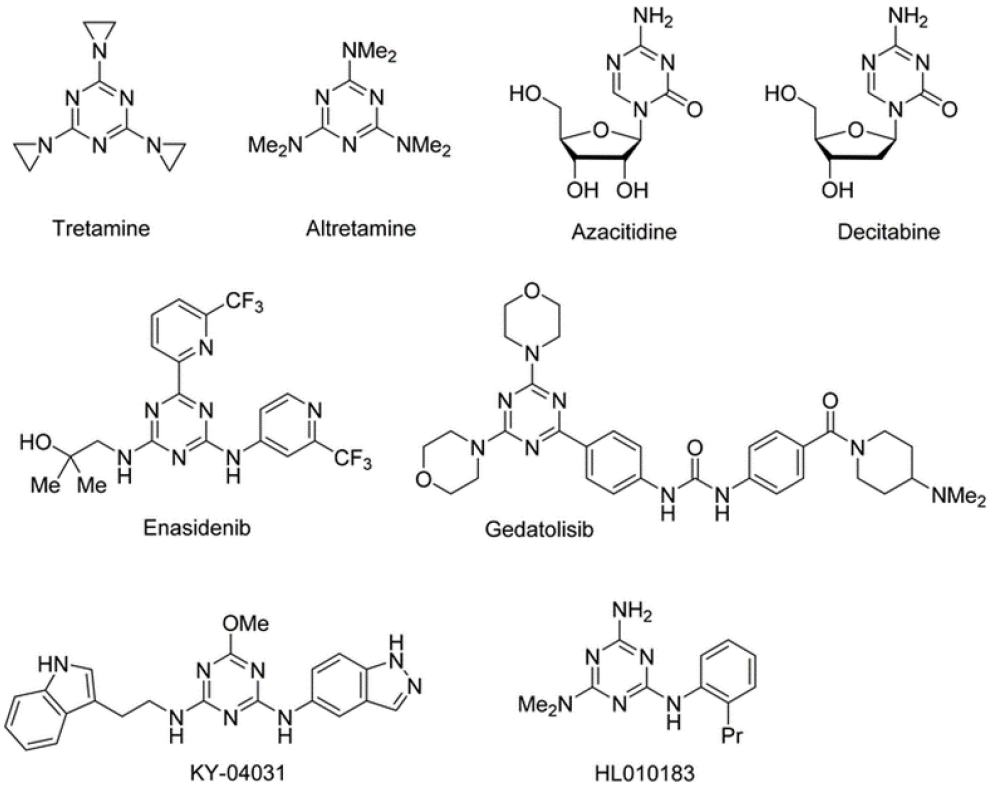


Figure 1. 1,3,5-triazine-based anticancer agents.

Benzotriazole (BtH) is a particularly versatile synthetic auxiliary because of its attractive properties. Benzotriazole can be easily inserted into molecules and can equally act as a good leaving group. Benzotriazole has both properties of a weak acid (pKa 8.2) as well as a weak base (pKa < 0), which enables its removal from the reaction by treating with either sodium carbonate solution (20%) or 4N hydrochloric solution. This molecule also shows electron-donating ability and electron-attracting ability, which leads to various synthetic applications. In 1980, benzotriazole was first reported as a synthetic auxiliary in organic chemistry [28]. Since then, benzotriazole has been used in the construction of various monocyclic and bicyclic heterocyclic compounds, which are difficult to prepare using other methods [29–34].

In addition, it has been found that microwave-assisted organic reactions are quicker and more effective because of the superheating effect and the ability of microwaves to rapidly heat reactions well above the solvent's boiling point. Microwave reactions are not only faster, but reactions themselves also reduce the amount of waste gas and liquid formation [35].

Benzotriazole chemistry has been practiced extensively in our group and has often been found to be superior to conventional routes [34]. In this communication, we report a novel synthetic route to tri-substituted 1,3,5-triazines through acyl benzotriazoles using no catalyst under heating conditions. The reaction gives quantitative yields and runs smoothly under either microwave or conventional heating. However, the best results are achieved when microwave irradiation is used as the source of heat. To the best of our knowledge, this is the first catalyst- and auxiliary-free and microwave-assisted synthesis of tri-substituted 1,3,5-triazines affording near quantitative yields under mild reaction conditions.

2. Results and Discussion

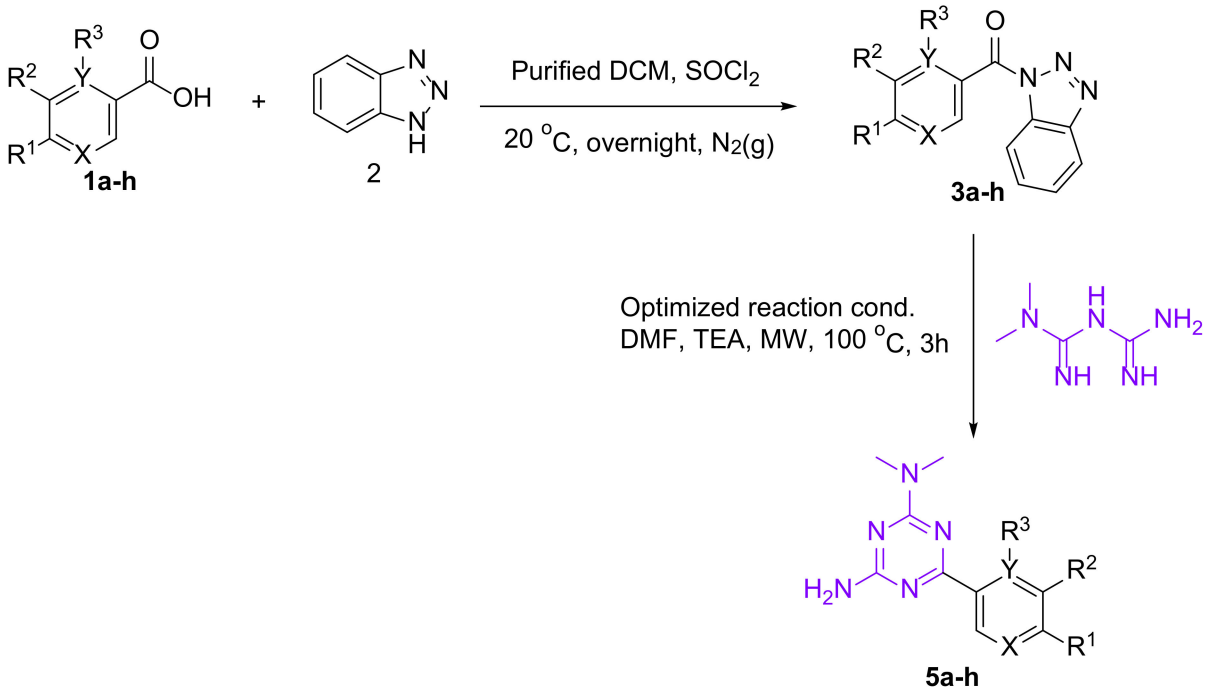
The carboxylic acid group of substituted benzoic acids (**1a–h**) was activated with 1H-benzotriazole (**2**) in the presence of $SOCl_2$ in purified DCM under nitrogen at room temperature by following our previously reported method [34]. Substituted benzoyl benzotriazolides (**3a–h**) were treated with metformin (**4**) by using our optimized reaction condition. Optimization of reaction conditions (Table 1) revealed the best results under microwave heating were at 100 °C for 3 h; conventional heating was less efficient.

Table 1. The reaction of benzoyl benzotriazolide with metformin in presence of TEA in DMF.

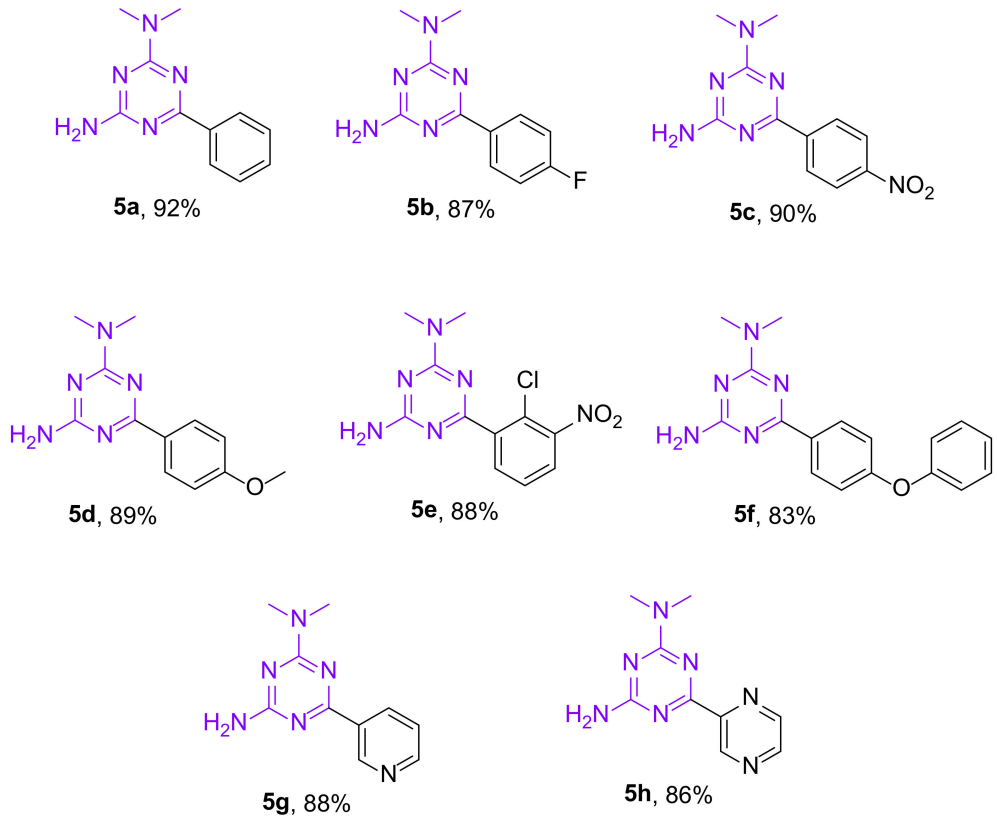
Entry	Reaction Temp. (°C)	Reaction Time (h)	Yield [a] (%)
1	20 (Room temp.)	24	0
2	100 (Conv.)	12	5
3	100 (Conv.)	24	25
4	70 (MW)	1	42
5	100 (MW)	1	65
6	100 (MW)	3	72

[a] Isolated yield.

In addition to reaction time and heating methods, we also explored different bases, such as triethylamine (TEA), diisopropylethylamine (DIPEA), 1,8-Diazabicyclo(5.4.0)undec-7-ene, and isobutyl chloroformate (IBCF), for the synthesis of tri-substituted 1,3,5-triazines. We successfully optimized the reaction condition and synthesized eight tri-substituted 1,3,5-triazines (**5a–h**) (Scheme 1). The work-up of the reactions was simple because the only byproduct formed was benzotriazole, which was easily removed by washing with sodium carbonate solution. All the triazines were fully characterized by spectral studies (supporting information).



Scheme 1. *Cont.*

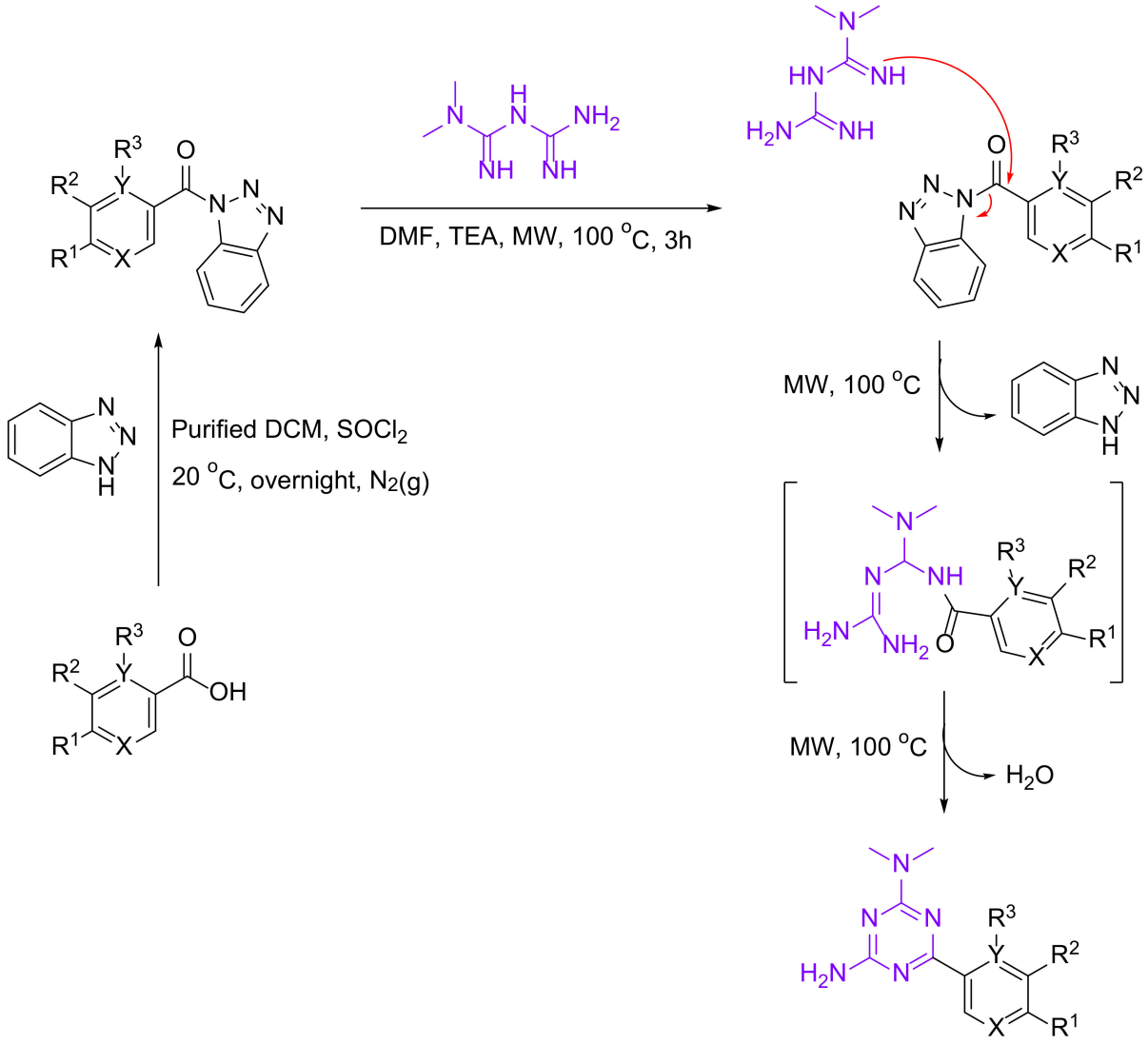


Scheme 1. Synthesis of tri-substituted 1,3,5-triazines.

A possible mechanism was proposed for the benzotriazole-mediated synthesis of 1,3,5-triazines from biguanides with aryl acids (Scheme 2). Benzotriazole was used to activate the carboxylic group of aryl acids. The activated aryl acids further reacted with metformin (a biguanide) and an acylation reaction takes place due to the leaving group property of the benzotriazole. Now, the acylated intermediate undergoes cyclization (condensation reaction) leaving a water molecule. The combination of benzotriazole and microwave chemistry promoted the formation of the desired tri-substituted 1,3,5-triazines in good yield and purity.

Computational Results

To assess the biological activity of the synthesized hybrid conjugates, StarDrop computation software [36] was used to calculate the pharmacokinetic properties of each derivative shown in Table 2. The Lipinski rule of five is often utilized to determine the viability of drug candidates. According to this rule, the drug candidates' pharmacokinetic properties must have Log P $\leq$ 5, MW $\leq$ 500, HBD $\leq$ 5 and HBD $\leq$ 10 to be considered for further study. For all metformin analogs, the Log P values improved over 10-fold, suggesting that there will be a considerable improvement in the analog ability to be absorbed through membranes. All derivatives fall within the limits of the Lipinski rule of five and, therefore, should be viable candidates.



Scheme 2. Plausible reaction mechanism.

Table 2. Calculated pharmacokinetics of metformin derivatives.

Compound	Log P	hERG pIC50	BBB Category	HIA Category	MW	HBD	HBA	Rotatable Bonds
5a	1.96	4.489	–	+	215	1	5	2
5b	1.88	4.866	–	+	233	1	5	2
5c	2.21	4.514	–	+	260	1	8	3
5d	2.1	4.665	–	+	245	1	6	3
5e	2.14	4.438	–	+	295	1	8	3
5f	3.18	5.116	–	+	307	1	6	4
5g	1.40	4.213	–	+	216	1	6	2
5h	1.35	4.372	–	+	217	1	7	2
Metformin	-0.36	2.912	–	+	129	4	1	3

It is widely accepted that a hERG pIC_{50} value ≤ 5 is considered safe. When viewing the hybrid conjugate hERG pIC_{50} values under this computational lens, there is only one derivative that violates this range, 4-phenoxy-benzoic-metformin (**5f**). However, this should not discount it from being considered a drug candidate because these guidelines help predict how it will behave in the body and are not always indicative of the biological activity in vivo.

The blood–brain barrier category (BBB) is expected to be negative for all derivatives indicating that the following drug cannot cross to the brain to affect it, as the brain is not targeted for therapeutic intervention for these metformin analogs. Table 2 shows that none of the derivatives can cross this barrier. The human intestinal absorption (HIA) category is another critical category to consider, especially when attempting to improve a molecule's bioavailability. All the metformin analogs are positive for this category and, therefore, are predicted to be absorbed in the intestines.

MW, HBD, HBA, and rotatable bonds are all physical properties of molecules that control a drug's interactions with its protein target. The viability of these derivatives in terms of MW, HBA, and HBD is within the limits of the rule of five parameters. Generally, rotatable bonds ≤ 10 are within an acceptable range per the Verber rule. All synthesized derivatives are within these ranges.

3. Conclusions

Benzotriazole chemistry has been practiced extensively in our group and has often been found to be superior to conventional routes. Using the acyl-substituted benzotriazole **3a**–**g** with the biguanide metformin under optimized microwave-assisted conditions, we report a novel synthetic route of eight tri-substituted 1,3,5-triazines in excellent yield. The methodology is the first, to our knowledge, that is a catalyst- and auxiliary-free and microwave-assisted synthesis of tri-substituted 1,3,5-triazines under mild reaction conditions. The resulting derivatives should be considered for biological studies as they follow the Lipinski rule of five guidelines and the Verber rule. **5f** shows higher-than-accepted hERG pIC_{50} values; however, it is only slightly over the accepted maximum of 5 and, therefore, should still be considered. There was over a ten-fold increase in Log P of the derivatives compared to metformin, suggesting that they may have improved bioavailability, which may make them biologically important drug candidates.

4. Experimental Section

Melting points were determined on a capillary tube melting point apparatus equipped with a digital thermometer. NMR spectra were recorded in DMSO-d_6 on a Bruker NMR spectrometer operating at 500 MHz for 1H (with TMS as an internal standard) and 125 MHz for 13C. HPLC-HRMS analyses were performed on reverse phase gradient using Agilent (Santa Clara, CA) 1200 series binary pump (G1312B), waters XTerra MS C18 (3.5 mm; 2.1–150 mm) þ Phenomenex C18 security guard column (2–4 mm) using 0.2% acetic acid in H_2O/methanol as mobile phases; wavelength $\frac{1}{4}$ 254 nm; and mass spectrometry was performed with 6220 Agilent (Santa Clara, CA, USA) TOF in electrospray ionization (ESI) mode with a positive and negative method in both Profile and Centroid mode.

5. Synthesis of Tri-Substituted 1,3,5-Triazines

Benzotriazole-activated substituted benzoic acids (1.5 mol), metformin (1 mmol), and triethylamine (TEA; 5 equiv.) were dissolved in dimethylformamide (DMF; 3 mL). The mixture was irradiated for 3 h at 100 °C. The crude mixture was poured over ice and stirred in sodium carbonate for 15 min. A white solid (72%) was isolated and purified by allowing the solid to stir for 30 min in diethyl ether. Vacuum filtration of the solvent yielded the pure desired product.

N,N-Dimethyl-6-phenyl-1,3,5-triazine-2,4-diamine (**5a**)

White crystalline solid, Yield: 92%; m.p. 163–165 °C; IR (ATR, cm^{-1}) 3336, 3186 (NH_2), 1659, 1573, 1505, 1381. ^{1}H-NMR ($CDCl_3$) δ: 8.38 (d, J = 7.0 Hz, 2H, Ar-H), 7.52–7.44 (m, 3H, Ar-H), 5.20 (s, 2H, $N\underline{H}_2$), 3.32 (s, 3H, $NC\underline{H}_3$), 3.19 (s, 3H, $NC\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 170.7, 167.0, 165.8, 137.0, 131.3, 36.2 ($N\underline{C}H_3$). HRMS m/z for $C_{11}\underline{H}_{13}N_5$ $[M + H]^+$ Calcd. 215.1171. Found: 215.1179.

6-(4-Fluorophenyl)-2-N,2-N-dimethyl-1,3,5-triazine-2,4-diamine (**5b**)

White crystalline solid, Yield: 87%; m.p. 121–123 °C; IR (ATR, cm^{-1}) 3492, 3344 (NH_2), 3232, 2915, 1556, 1533, 1388. ^{1}H-NMR (DMSO-d_6) δ: 8.35 (t, J = 8.8 Hz, 2H, Ar-H), 7.30

(t, *J* = 8.8 Hz, 2H, Ar-H), 6.87 (s, 2H), 3.20 (s, 3H, NCH$_3$), 3.10 (s, 3H, NCH$_3$). ^{13}C-NMR (DMSO-d_6) δ: 168.8, 167.4, 166.0, 165.6, 163.6, 134.1, 130.6, 130.5, 115.6, 115.5, 36.2 (NCH$_3$). HRMS m/z for $C_{11}H_{12}FN_5$ $[M + H]^+$ Calcd. 233.1077. Found: 233.1074.

6-(4-Nitrophenyl)-2-N,2-N-dimethyl-1,3,5-triazine-2,4-diamine (**5c**)

White crystalline solid, Yield: 90%; m.p. 179–181 °C; IR (ATR, cm^{-1}) 3492, 3343 (NH$_2$), 3232, 2925, 1649,1556, 1529, 1387. ^{1}H-NMR (DMSO-d_6) δ: 8.51 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.34 (d, *J* = 8.9 Hz, 2H, Ar-H), 3.18 (s, 3H, NCH$_3$), 3.11 (s, 3H, NCH$_3$). ^{13}C-NMR (DMSO-d_6) δ: 168.1, 167.5, 165.9, 143.7, 129.3, 123.9, 32.3 (NCH$_3$), 36.2 (NCH$_3$). HRMS m/z for $C_{11}H_{12}N_6O_2$ $[M + H]^+$ Calcd. 260.1022. Found: 260.1025.

6-(4-Methoxyphenyl)-2-N,2-N-dimethyl-1,3,5-triazine-2,4-diamine (**5d**)

White crystalline solid, Yield: 89%; m.p. 187–189 °C; IR (ATR, cm^{-1}) 3336, 3172 (NH$_2$), 2934, 1526, 1504, 1377 (OCH$_3$), 1029. ^{1}H-NMR ($CDCl_3$) δ: 8.36 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.97 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.20 (s, 2H, NH$_2$), 3.89 (s, 3H, -OCH$_3$), 3.31 (s, 3H, NCH$_3$), 3.18 (s, 3H, NCH$_3$). ^{13}C-NMR ($CDCl_3$) δ: 170.0, 166.8, 165.1, 162.4, 130.0, 129.3, 113.5, 55.4 (OCH$_3$), 36.2 (N(CH$_3$)$_2$). HRMS m/z for $C_{12}H_{15}N_5O$ $[M + H]^+$ Calcd. 245.1277. Found: 245.1281.

6-(2-Chloro-3-nitrophenyl)-2-N,2-N-dimethyl-1,3,5-triazine-2,4-diamine (**5e**)

White crystalline solid, Yield: 88%; m.p. 143–145 °C IR (ATR, cm^{-1}) 3457 (NH$_2$), 3296, 3140, 1638, 1573, 1506, 1349. ^{1}H-NMR (DMSO-d_6) δ: 8.09 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.87 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.67 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.06 (s, 2H, NH$_2$), 3.09 (s, 6H, N(CH$_3$)$_2$). ^{13}C-NMR (DMSO-d_6) δ: 170.5, 167.0, 165.3, 149.8, 140.5, 133.9, 128.8, 125.5, 122.9, 36.3 (NCH$_3$), 36.1 (NCH$_3$). HRMS m/z for $C_{11}H_{11}ClN_6O_2$ $[M + H]^+$ Calcd. 294.0632. Found: 294.0633.

6-(4-Phenyloxyphenyl)-2-N,2-N-dimethyl-1,3,5-triazine-2,4-diamine (**5f**)

White crystalline solid, Yield: 83%; m.p. 169–171 °C; IR (ATR, cm^{-1}) 3327, 3182 (NH$_2$), 1571, 1521, 1487, 1386 (C_6H_4-O-C_6H_5), 1232. ^{1}H-NMR ($CDCl_3$) δ: 8.35 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.36 (t, *J* = 8.0, 2H, Ar-H), 7.14 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.06–7.02 (m, 4H, Ar-H), 5.04 (s, 2H, NH$_2$), 3.28 (s, 3H, NCH$_3$), 3.16 (s, 3H, NCH$_3$). ^{13}C-NMR ($CDCl_3$) δ: 170.3, 167.3, 165.9, 160.2, 156.6, 132.0, 130.1, 129.8, 123.8, 119.4, 117.9, 36.2 (N(CH$_3$)$_2$). HRMS m/z for $C_{17}H_{17}N_5O$ $[M + H]^+$ Calcd. 307.1433. Found: 307.1429.

2-N,2-N-Dimethyl-6-pyridin-3-yl-1,3,5-triazine-2,4-diamine (**5g**)

White crystalline solid, Yield: 88%; m.p. 168–170 °C; IR (ATR, cm^{-1}) 3493, 3343 (NH$_2$), 3231, 2926, 1714, 1556, 1387. ^{1}H-NMR (DMSO-d_6) δ: 9.41 (s, 1H, Ar-H), 8.71–8.69 (m, 1H, Ar-H), 8.57–8.54 (m, 1H, Ar-H), 7.53–7.50 (m, 1H, Ar-H), 6.96 (s, 2H, NH$_2$), 3.21 (s, 3H, NCH$_3$), 3.11 (s, 3H, NCH$_3$). ^{13}C-NMR (DMSO-d_6) δ: 207.0, 168.5, 167.3, 165.8, 152.2, 149.6, 135.6, 133.0, 123.9, 31.2 (N(CH$_3$)$_2$). HRMS m/z for $C_{10}H_{12}N_6$ $[M + H]^+$ Calcd. 216.1123. Found: 216.1129.

2-N,2-N-Dimethyl-6-pyrazin-2-yl-1,3,5-triazine-2,4-diamine (**5h**)

White crystalline solid, Yield: 86%; m.p. 253–255 °C; IR (ATR, cm^{-1}) 3293 (NH$_2$), 3068, 1572, 1506, 1392, 1211. ^{1}H-NMR (DMSO-d_6) δ: 9.34 (d, *J* = 2.4 Hz, 1H, Ar-H), 8.76 (d, *J* = 2.4 Hz, 1H, Ar-H), 8.72 (s, 1H, Ar-H), 5.20 (s, 2H, NH$_2$), 3.43 (s, 3H, NCH$_3$), 3.42 (s, 3H, NCH$_3$). ^{13}C-NMR (DMSO-d_6) δ: 166.3, 163.1, 162.6, 147.6, 145.7, 145.0, 144.0, 36.4 (NCH$_3$), 36.3 (NCH$_3$). HRMS m/z for $C_9H_{11}N_7$ $[M + H]^+$ Calcd. 217.1076. Found: 217.1082.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/reactions3040034/s1.

Author Contributions: Conceptualization, S.S.P.; methodology, E.T., A.M.P. and S.S.P.; software, E.T. and S.S.P.; investigation, S.S.P.; resources, E.T. and S.S.P.; data curation, E.T. and A.M.P.; writing—original draft preparation, E.T. and S.S.P.; writing—review and editing, E.T., A.M.P. and S.S.P.; supervision, S.S.P.; project administration, S.S.P. All authors have read and agreed to the published version of the manuscript.

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