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RESEARCH ARTICLE

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Imidazotetrazines as Weighable Diazomethane Surrogates for Esterifications and Cyclopropanations

Riley L. Svec and Paul J. Hergenrother*[a]

Abstract: Diazomethane is one of the most versatile reagents in organic synthesis, but its utility is limited by its hazardous nature. Although alternative methods exist to perform the unique chemistry of diazomethane, these suffer from diminished reactivity and/or correspondingly harsher conditions. Here we describe the repurposing of imidazotetrazines (such as temozolomide, TMZ, the standard of care for glioblastoma) for use as synthetic precursors of alkyl diazoniums. TMZ is employed to conduct esterifications and metal-catalyzed cyclopropanations, and results show that methyl ester formation from a wide variety of substrates is especially efficient and operationally simple. TMZ is a commercially available solid that is non-explosive and non-toxic, and should find broad utility as a replacement for diazomethane.

Introduction

As a C_1 synthon, diazomethane (Figure 1a) is one of the most versatile reagents in synthetic organic chemistry.[1,2] While best known for its ability to rapidly methylate carboxylic acids, diazomethane can also methylate other nucleophiles under mild conditions, and its powerful reactivity is further extended to homologations, [3+2] cycloadditions, and metal-catalyzed cyclopropanations. Because of this reactivity, diazomethane is notoriously hazardous to handle; even when used as a dilute solution with specialized glassware (flame-polished, no ground glass joints), the reagent is exceptionally sensitive to heat, shock, light, and explosively decomposes. Diazomethane is also acutely toxic to humans[3,4] with an OSHA permissible exposure limit of 0.2 ppm,[5] and its toxicity is exacerbated by its volatility (boiling point = –23°C).

The formidable hazards of diazomethane have severely limited its routine laboratory use and instead diazomethane substitutes, such as trimethylsilyldiazomethane (TMS-diazomethane, Figure 1a), are typically employed. TMS-diazomethane is commercially available as a 2 M solution in ether or hexanes, however, it is a much weaker nucleophile than diazomethane, diminishing its reactivity in many cases.[6,7] Though TMS-diazomethane is less prone to explosive decomposition compared to diazomethane, it must still be handled with utmost caution as inhalation can induce fatal respiratory toxicity including pulmonary edema.[8] If required, diazomethane can be generated on preparative scales from *N*-methyl-*N*-nitroso precursors. The most widely used is Diazald (Figure 1a), which upon treatment with ≥6 M KOH and distillation with specialized glassware can yield an ethereal solution of diazomethane suitable for subsequent reactions;[1,9,10] this procedure, however, is far from user-friendly as the compound is still prone to explosion during distillation and storage.

Convenient methods to prepare and react larger, stabilized diazoalkane species *in situ* have been reported,[11–13] but few generate diazomethane itself. Flow chemistry is well-suited for the continuous supply and consumption of dangerous reactants, and indeed, many reports have detailed the development of such systems that can safely generate and react diazomethane over time with high yields,[14–19] but alternative means to safely exploit the reactivity of diazomethane in batch reactions are still needed. Perhaps the simplest approach on this front has been to distill diazomethane directly into a reaction mixture. This procedure avoids the isolation of diazomethane but requires complex experimental setups and air-free conditions.[20–22] Another elegant approach, pioneered by Carreira, uses a water-soluble version of Diazald (**1**, Figure 1a) to generate diazomethane and react it with olefins in the same flask by establishing a biphasic reaction mixture.[23] Its practicality for *in situ* diazomethane generation in a non-flow setting is remarkable; however, the conditions still require the use of 6 M KOH to form diazomethane from the nitroso precursor. As such, this method is limited to one transformation (cyclopropanation) under very specific constraints. Without the mild reaction conditions that make diazomethane so effective, most reactions (including esterifications) are not feasible with this methodology. Thus, new reagents that generate diazomethane or methyl diazonium *in situ* and consume it in subsequent reactions would be extremely valuable.

The imidazotetrazine class of molecules was first reported in 1984 and feature a 1,2,3,5-tetrazin-4-one motif.[24] The most well-known member of this class is temozolomide (TMZ, Figure 1a), which serves as the standard of care for glioblastoma (GBM).[25,26] TMZ hydrolyzes spontaneously at physiological pH, ring-opening to triazene intermediate MTIC, which then rapidly releases the active methylating component, methyl diazonium (Figure 1b),[27,28] leading to methylation of DNA in tumor cells. The half-life of TMZ in aqueous media *in vitro* (at pH 7.4, 37°C) and *in vivo* is ~2 hours.[27,29–31] Other features that contribute to TMZ's success as a therapeutic include its water solubility, robust synthesis providing a remarkably stable solid, and excellent tolerability (patients receive ~250–320 mg TMZ during one round of treatment). The unique activation mechanism of imidazotetrazines, releasing methyl diazonium slowly over time in water, suggested to us that they may have utility in chemical synthesis as solid state precursors to diazoalkane species. Herein, we repurpose imidazotetrazine prodrugs into organic reagents to efficiently conduct the two most widely used reactions of diazomethane, esterifications and cyclopropanations.

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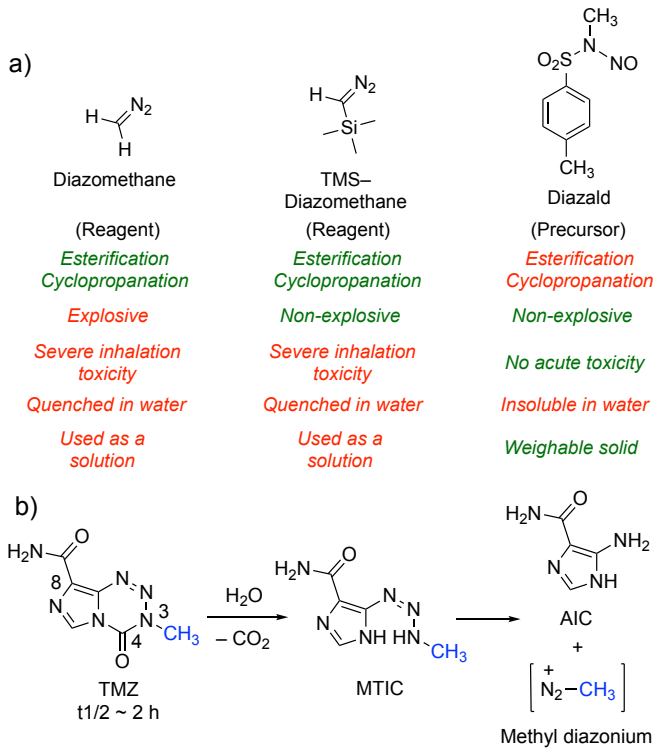
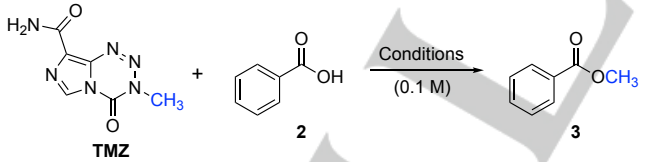


Figure 1. (a) Comparison of diazomethane, TMS-diazomethane, and select diazomethane precursors, with favorable features in green and unfavorable features in red. (b) Mechanism of hydrolysis of TMZ to methyl diazonium. MTIC = 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide; AIC = 4-amino-5-imidazolecarboxamide.

Results and Discussion

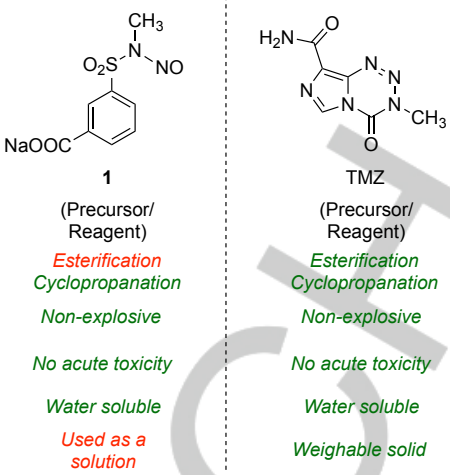
To start our investigation, we surveyed conditions to methylate benzoic acid. We hypothesized that water would prove essential in this reaction to promote the hydrolysis of TMZ, but that an organic solvent would also be necessary for substrate dissolution. The initial successful reaction, yielding an 8% conversion of benzoic acid **2** to methyl benzoate **3**, was obtained

Table 1. Esterification reaction using TMZ

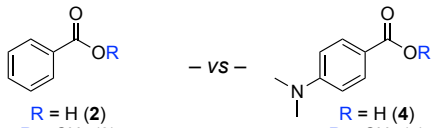


Entry	eq. TMZ	Temp.	Additive	Time (h)	Solvent	% Conversion
1	1	23	Na_2CO_3	4	1:1 ACN:H_2O	8%
2	1	23	–	4	1:1 ACN:H_2O	0%
3	1	60	Na_2CO_3	4	1:1 ACN:H_2O	12%
4	1	60	Na_2CO_3	6	1:1 ACN:H_2O	11%
5	1	60	Na_2CO_3	4	100% ACN	0%
6	1	60	Na_2CO_3	4	1:1 Diox:H_2O	20%
7	1	60	Na_2CO_3	4	9:1 Diox:H_2O	47%
8	2	60	Na_2CO_3	4	9:1 Diox:H_2O	68%

Conversion (%) was determined by HPLC comparing the ratio of methyl benzoate to benzoic acid (see Supplementary Information for more details). ACN = acetonitrile; Diox = 1,4-dioxane.



after 4 hours with one equivalent of TMZ at room temperature with equal parts water and acetonitrile as cosolvents (Table 1, Entry 1). The addition of sodium carbonate as a deprotonation agent proved necessary as no conversion was observed under identical conditions without base (Table 1, Entry 2). Increasing the temperature of the reaction to 60°C was advantageous, presumably facilitating the quantitative hydrolysis of TMZ (Table 1, Entry 3); however, extending the reaction time to 6 hours did not facilitate more product conversion (Table 1, Entry 4). Water was indeed critical to the reaction as no esterification occurred in acetonitrile alone (Table 1, Entry 5). 1,4-dioxane proved the most suitable solvent (Table 1, Entry 6) and biasing the ratio of organic solvent to water to 9:1 (Table 1, Entry 7) led to a sizeable improvement in product formation; it is likely that reducing the proportion of water in favor of a non-nucleophilic solvent increases the lifetime of the methyl diazonium. The addition of two equivalents of TMZ led to a 68% conversion of benzoic acid to the esterified product (Table 1, Entry 8). These final reaction conditions proved exceptionally practical as all of the solid reagents (TMZ, substrate, and base) could be added at the outset of the reaction, avoiding the need for the slow addition required when using diazomethane or TMS-diazomethane. Additionally, the reactions proceeded open to air.



Conditions	Yield **3** (%)
a	54%
b	70%

Conditions	Yield **5** (%)
a	74%
b	88%

Figure 2. Comparison of esterification reaction using different substrates and conditions. Conditions a: 2 eq. TMZ, 4 eq. Na_2CO_3, 9:1 Diox:H_2O, 60°C, 4 h. Conditions b: 2 eq. TMZ added initially, 2 eq. TMZ added after 2 h, 4 eq. Na_2CO_3, 9:1 Diox:H_2O, 60°C, 6 h.

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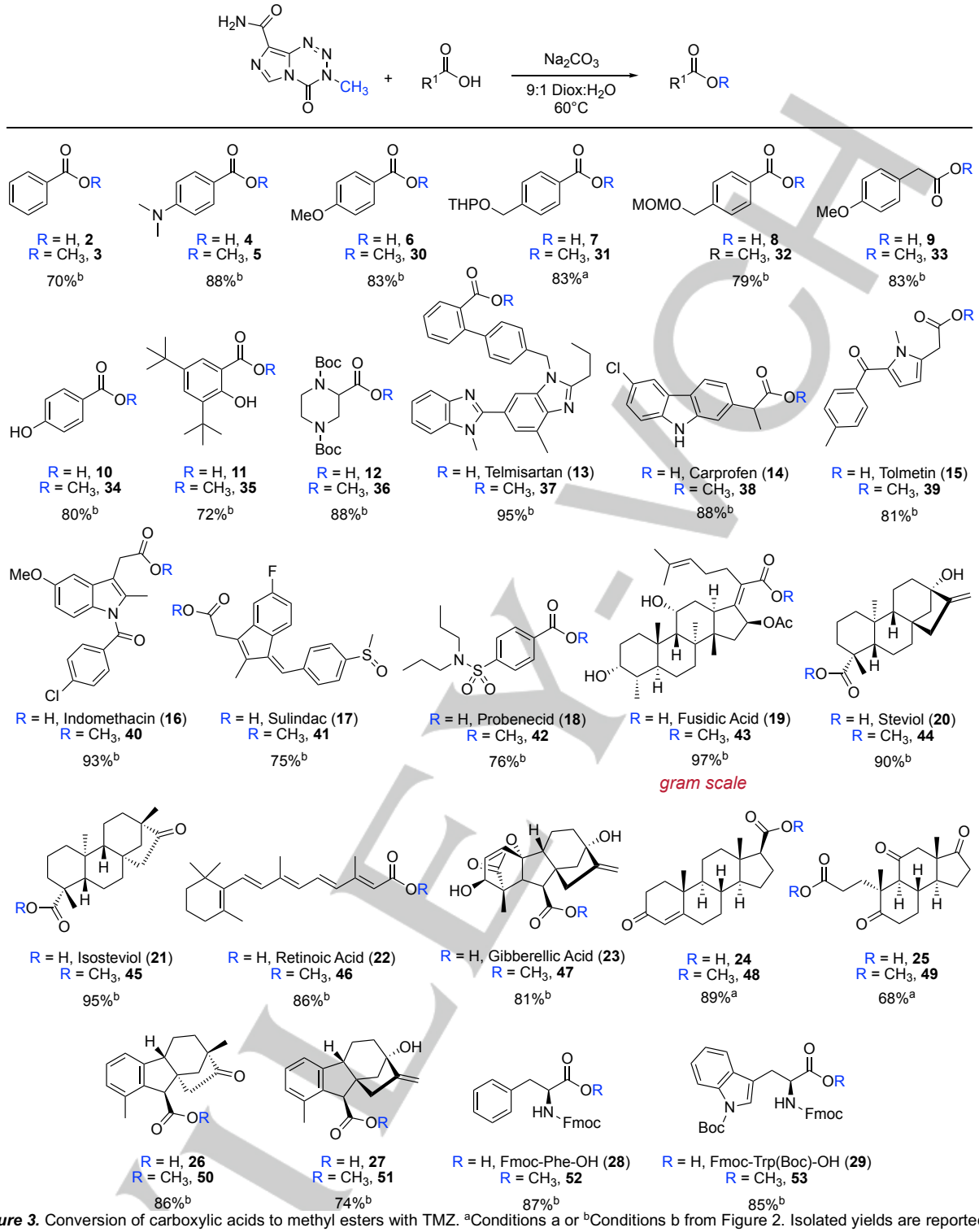

Figure 3. Conversion of carboxylic acids to methyl esters with TMZ. [a]Conditions a or [b]Conditions b from Figure 2. Isolated yields are reported, 0.15–1 mmol scale unless otherwise noted. THP = tetrahydropyran; MOM = methoxymethyl; Boc = tert-butyloxycarbonyl; Ac = acetyl; Fmoc = fluorenylmethoxycarbonyl.

The modest conversion of benzoic acid to methyl benzoate under the optimized reaction conditions prompted a study of potential product saponification given the mildly basic, aqueous milieu. Subjecting methyl benzoate to the reaction conditions (absent TMZ), however, did not lead to any discernable benzoic acid formation after 4 hours (Figure S1), suggesting a negligible role of saponification on the conversion. Importantly, as the residual material in the reaction is solely unconverted starting material, the isolated yield could be improved from 54% to 70% simply by adding more TMZ and extending the reaction time to 6 hours (Figure 2). The need for more equivalents of TMZ than would be required of diazomethane itself (typically ≤1.5 equivalents)[18] suggests less efficient trapping of methyl diazonium by the substrate when generated from TMZ. Furthermore, product formation proved dependent on the

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electronics of the acid substrate as an 88% yield of **5** was obtained from more electron-rich benzoic acid analog **4**.

To explore the generality and mildness of this reaction, we investigated the methylation of diverse compounds including many drug/drug-like and natural product/natural product-like compounds bearing carboxylic acids (Figure 3). The acid-sensitive THP and MOM ethers of **7** and **8** may not be tolerated under common Fischer esterification conditions (for example), but are well-tolerated by this method. The esterification of 4-methoxyphenylacetic acid (**9**) proceeded with yields comparable to its electron-rich benzoic acid counterpart **6**. Phenols were also tolerated with this methodology as appreciable yields of monofunctionalized ester products **34** and **35** were afforded from compounds **10** and **11**, respectively. Similarly, Boc groups were tolerated as piperazine substrate **12** was esterified to **36** in ~90% yield with no deprotected byproducts observed. Pharmaceuticals **13**–**18** and natural products **19**–**23** containing an array of peripheral functional groups were all converted to the corresponding methyl ester directly from the parent compound without the need for extreme temperatures, coupling reagents, or strong acid. Fusidic acid (**19**) was esterified on a gram scale with a 97% isolated yield, demonstrating the ready scalability of these reactions. This example further showcases the selectivity of this method for carboxylic acids over other functional groups (such as alcohols) as methylation occurs at the acid in the presence of two secondary alcohols. Steroid metabolite **24**, natural product-derived compounds **25** (from adrenosterone)[32] and **26**–**27** (from gibberellic acid)[32], and protected amino acids **28**–**29** were also effectively esterified. The esterification of this diverse collection of compounds illustrates the mildness of these conditions as often labile functional groups such as olefins, esters, acetates, sulfonamides, ketones, and enones were compatible in this context. Furthermore, these reactions take ≤6 hours and products are conveniently purified through a silica gel plug as the only byproduct of TMZ, AIC (Figure 1b), and the starting material are both retained on silica.

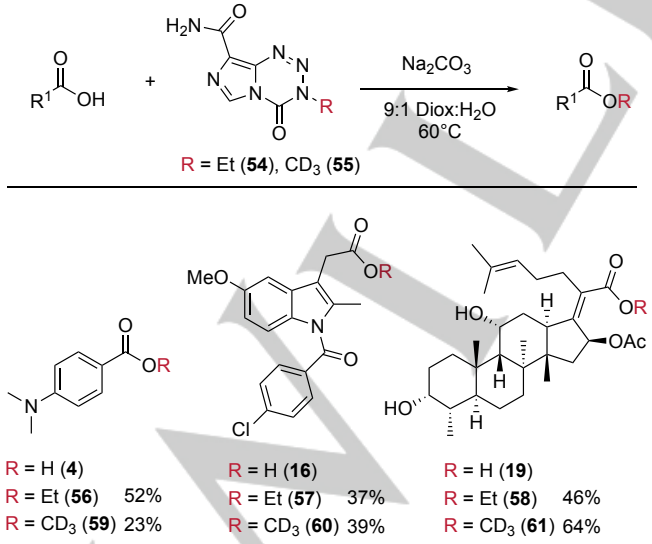

Figure 4. Esterification of carboxylic acids with N3-substituted imidazotetrazines **54** and **55**. H_2O was replaced with D_2O in reactions to form **59**–**61**. Isolated yields are reported, 0.15 mmol scale.

A distinct advantage of imidazotetrazines is the modularity of their syntheses. The alkylating moiety at N3 may be readily exchanged by reacting 4-diazoimidazole-5-carboxamide with the desired isocyanate. Though the N3-methyl variant (TMZ) exhibited the most anticancer efficacy, dozens of other N3-modifications have been reported including ethyl, methoxymethyl, and propargyl.[24,33,34] As an initial exploration into the use of differentially-substituted imidazotetrazines to generate esters beyond methyl, we synthesized the N3-ethyl and N3-CD_3 imidazotetrazines and reacted each with **4**, **16**, and **19**, providing rapid access to the corresponding esters (Figure 4). The lower yields of ethyl esterification compared to the corresponding methyl esterification are likely a result of the competing elimination pathway possible for ethyl diazonium but not methyl diazonium. Nonetheless, the ethyl ester of fusidic acid (**58**) was formed with a 46% isolated yield using this method; the only prior synthesis of this analog yielded product in 9% after a Steglich esterification.[35] Novel trideuteromethyl esters **59**–**61** were furnished in modest yields; D_2O was substituted in the reaction mixture to inhibit D/H exchange by the alkylating species.

Beyond alkylations, diazo compounds can be employed to form cyclopropanes from alkenes in the presence of metals. Acceptor-substituted diazo reagents such as ethyl diazoacetate are commercially available, stable, and versatile, but diazomethane is unique in its competency to form unsubstituted cyclopropanes in high yields. The only batch system able to generate and react diazomethane *in situ* is the water-soluble version of Diazald (compound **1**, Figure 1a) that can facilitate the iron-catalyzed cyclopropanation of olefins in 6 M aqueous KOH.[23] While a significant advance, **1** must be synthesized using harsh conditions (requiring a blast shield) and ultimately added slowly as a solution over 4+ hours. A safe, convenient method to generate diazomethane *in situ* from a solid reagent weighed at the outset of the reaction would be a highly desirable, practical advance in metal-mediated cyclopropanations.

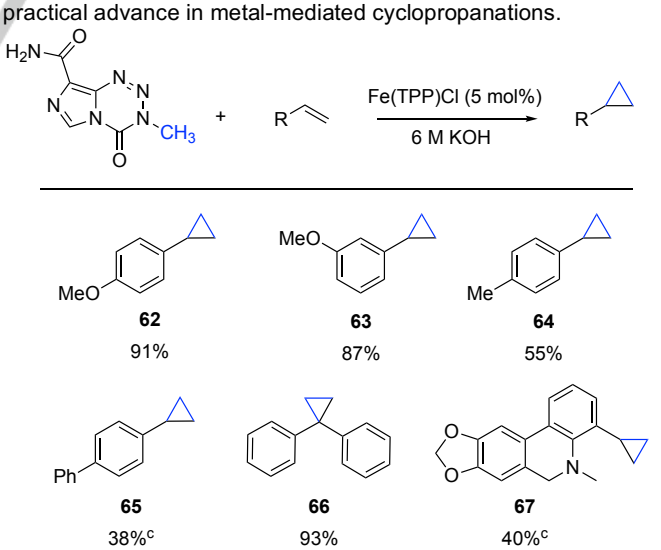

Figure 5. Metal-catalyzed cyclopropanation reaction with TMZ. Reaction conditions: substrate (0.2 mmol), TMZ (0.6 mmol), Fe(TPP)Cl (0.008 mmol), 6 M KOH (0.5 mL). Fe(TPP)Cl = 5,10,15,20-tetraphenyl-*21*H,*23*H-porphine iron (III) chloride. [c]Toluene was added to dissolve the solid substrate.

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Toward this end, the use of TMZ for metal-catalyzed cyclopropanations was explored. Employing 4-vinylanisole as a model substrate, mild conditions were initially evaluated. Only 6% conversion of 4-vinylanisole to 4-cyclopropylanisole was observed using 5 mol % Fe(TPP)Cl and the esterification conditions (Table S1, Entry 2). Several other transition metals (palladium, rhodium, copper) known to mediate cyclopropanations with diazo compounds did not afford any product. Proceeding with Fe(TPP)Cl, the dioxane/water solvent system was exchanged for aqueous KOH, which led to a significant increase in conversion (Table S1, Entries 6–7). It is probable that a more basic solution is required to facilitate the conversion of methyl diazonium to neutral diazomethane, which can diffuse to the organic layer and act as the source for the metallocarbene intermediate. Adding another equivalent of TMZ, decreasing the temperature of the reaction to ambient temperature, and increasing the concentration of the reaction improved the conversion to 93% (Table S1, Entry 10). TMZ effectively cyclopropanated several styrenyl (**62**–**66**) and natural product-derived (**67**)[36] substrates in 6 M KOH (Figure 5). More electron-rich substrates furnished better yields akin to other diazomethane-generating cyclopropanation methods.[23] Beyond electronics, solid substrates provided lower yields due to dilution of the organic phase with toluene, necessary for compound dissolution. The reactions were conducted open to air at room temperature and products were quantitatively separated from 4-amino-5-imidazolecarboxamide (AIC, Figure 1b) through an extraction.

Conclusion

TMZ's unique mechanism of activation and water solubility make it an exceptional generator of methyl diazonium under mild conditions, with subsequent methyl ester formation particularly efficient. TMS-diazomethane is frequently implemented as a less explosive diazomethane surrogate for esterification, but it retains lethal toxicity. Other methylating reagents such as methyl iodide, dimethyl sulfate, or dimethyl carbonate are commonly used for *O*-methylation, but are decisively less reactive often requiring harsh conditions (e.g. strong base or temperatures >100°C) and/or longer reaction times (12–24 hours).[37] TMZ serves as a complementary *O*-methylating reagent that has the advantages of being a solid, affordable (~$3.70/mmol vs. ~$6.30/mmol for a 2 M solution of TMS-diazomethane in diethyl ether) precursor to the methyl diazonium cation; in addition, the tolerability of this compound is well known as it is administered to cancer patients over months as a pharmaceutical. Since the tetrazinone motif masks the alkyl diazonium equivalent, TMZ also exhibits considerably more thermal stability than other diazomethane precursors like Diazald, which bears an *N*-methyl *N*-nitroso group; Diazald decomposes (explosively) at its melting point of 60°C,[38] while TMZ is stable up to its melting point, 212°C. It should be noted that, while more convenient than other diazomethane precursors, proper caution is still warranted (particularly on large scale) when employing TMZ in these reactions. Finally, chemical derivatives of imidazotetrazines are readily accessible; for example, we show that substitution at the N3 position, the site bearing the eventual alkylating moiety, can yield precursors of other esters, but substitutions at the C8 position are also attainable and have been demonstrated to tune the rate of hydrolysis.[29] With several significant advantages over other diazomethane precursors and its ready availability, TMZ should find broad utility in chemical synthesis.

Acknowledgements

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Keywords: Imidazotetrazine • Diazomethane • Alkylation • Cyclopropanation • Diazo compounds

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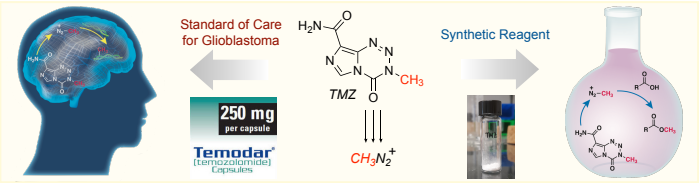

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Imidazotetrazines as Weighable Diazomethane Surrogates for Esterifications and Cyclopropanations

From patient to flask: Temozolomide (the standard of care for glioblastoma) and other imidazotetrazine compounds are repurposed into synthetic reagents. The prodrugs release alkyl diazonium species under aqueous conditions and are thus employed to conduct the two most widely used reactions of diazomethane, esterifications and cyclopropanations.

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