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Alternative method for the synthesis of triazenes from aryl diazonium salts

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ABSTRACT

An alternative mild method for access to 1-aryl-3,3-dimethyl alkyl triazenes is described. This protocol employs the dropwise addition of a methanolic solution of a carboxylate (RCO_2M) or carbonate (CO_3^{2-}) to a gently heated DMF solution containing an aryl diazonium salt (ArN_2^+), that had been previously isolated. Presumably homolysis of the weak N–O bond of diazo ether adducts formed in this operation initiates radical pathways that lead to the generation of triazene product. DMF serves as not only a one-electron donor to the diazonium salts employed in this process, but also as a source of dimethylamine radicals that act as a nucleophilic coupling partner. The reaction provides modest yields (ca. 20–40%) across an array of aryl diazonium salts that contain various substitution. Furthermore this unique approach to triazenes contrasts with traditional methods that employ dimethyl amine in reagent form which directly couples with diazonium salts. Seemingly, only one other example employing somewhat similar reaction conditions to this current investigation en route to triazenes has been reported, albeit with lower yields and for one representative example furnished as a side-product. The current work here improves upon the efficiency of this reported result, and further expands the reaction scope.

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1. Introduction

Triazenes are an important class of organic molecules that contain three contiguous nitrogen atoms, two of which comprise a double bond, commonly *trans*-configured, between N1 and N2 (Scheme 1). This functional group (–N (RR'')–N=N–) stems from its point of attachment to an aromatic or aliphatic moiety. Shown in Scheme 1 is the aryltriazene archetypical of the current study, an asymmetrical 1-aryl-3,3-dialkyl triazene (ArN=N-NRR″). Here, the pi electron delocalization leading to an important 1,3-dipolar zwitterionic resonance form is depicted.

What is more, the nature of the substituent(s) R′ on the aryl ring connected to the triazene functionality greatly impact the relative contributions of these resonance structures. In this vein, the mesomeric effects transmitted through the molecule become especially prominent in the case of attached electron-withdrawing groups, which impart an increased rotational barrier around N2 and N3, as the N1 atom more effectively donates electron density to the ring [1]. Likewise, the 1,3-dipolar characteristics of aryltriazenes are supported by Hammett plot correlations of substituent effects and rotational rate constants, obtained via temperature dependent NMR analysis. These results have been found to correspond in a highly sensitive and quantitative fashion to variations in the appended functionality of the aryl ring [2].

Thermolysis experiments as determined by differential scanning calorimetry (DSC) clearly demonstrate that aryltriazenes exhibit greater thermal stability than their diazonium salt ($R'ArN_2^+$) counterparts. Here, the nature of the specific appended substituent(s) (R′) also plays an influential role in directing this characteristic. For instance, electron-withdrawing groups on the aryl ring impart a greater relative thermal stability compared to electron donating substituents [3], as is suggested by the zwitterionic resonance form of Scheme 1.

The greater inherent stability of triazenes has supported extensive investigations, as they are able to serve as shelf stable [3b] and chromatographically purifiable precursors to *in situ* formed diazonium salts [4] among other roles. Activation commences upon pairing of triazenes with protonating or alkylating agents, thus permitting the revelation of their latent reactivity at an appropriate synthetic juncture. This phenomenon is a major impetus for the implementation of triazenes towards various procedures including Sandmeyer-type and organometallic cross-coupling reactions [5], among other protocols. Regardless of the

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Scheme 1. 1-Aryl-3,3-Dialkyl Triazene Resonance Forms.

application, the liberation of a generated diazonium salt proceeding through *in situ* activation of triazenes minimizes the chance of forming undesired byproducts and demonstrates their potential synthetic advantage.

Other notable examples which illustrate the manipulation of these unique features are quite varied. For example, triazenes have been utilized as a protected equivalent of aryl halides en route to a variety of step-economical annulation strategies [6]. Triazene-bearing moieties have been designed as fruitful coupling partners for pericyclic reactions followed by post-coupling modifications [7] of the embedded triazene unit. Other cases in which triazenes have been unmasked *in situ* and subsequently utilized as diazonium salt surrogates in organometallic cross-coupling [8] and in metal-free cross-coupling protocols [9] are noteworthy. In the burgeoning field of C—H activation, the triazene unit as a component of a tosyl reagent unveiling latent reactivity at an appropriate synthetic stage has been invented [10].

In serving as concealed diazonium salts, with stability towards various reagents, triazenes have also been employed successfully as cleavable linkers in combinatorial chemistry with applications toward drug discovery [11,12]. From a material science perspective, the immobilization of aryl triazenes have been explored as a tool for surface patterning [13]. Triazenes have been employed with useful application toward novel heterocyclic systems, including indoles, isoindazoles, cinnolines, and triazoles [4,14]. Finally, triazenes are employed as functionalized ligands in organometallic chemistry. For example, in conjunction with nickel ions they have been incorporated as triazenido ligands and adopted as a new electrocatalyst for hydrogen generation [15]. While in analytical chemistry triazenes have been utilized as highly sensitive and selective optical sensors for determination of mercury (II) ions in aqueous solutions [16].

Triazenes have likewise been investigated for biological applications, including anti-cancer therapies. Triazenes can serve as prodrugs, being able to convert in the body to a physiologically activated species. These resulting monomethyl species and/or their spontaneously released methyl diazonium reactive intermediates can subsequently alkylate DNA and RNA, most significantly at the O^6 and N^7 positions of guanine [4,17]. Once methylated, the DNA strands stick together as inter-strand cross-links which inhibit DNA reduplication, and suppress RNA and protein synthesis.

Commercially available triazenes acting as cytotoxic "prodrugs" that operate through this *in situ* mode of biological activation include temozolomide (TMZ) and dacarbazine, also known as 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC). Both of these commercially available drugs generate 3-methyl-(triazen-1-yl)-imidazole-4-carboxamide (MTIC), as the cytotoxic metabolite. DTIC for example forms MTIC by way of P450-catalyzed *N*-dealkylation of *N*,*N*-dimethyl-triazenes [18]. This monomethyl triazene active metabolite [19] develops from DTIC by means of a process that first generates a hydroxymethyl triazene, 5-[3-hydroxymethyl-3-methyl-triazen-1-yl]-imidazole-4-carboxamide (HMMTIC), followed by loss of formaldehyde [20].

Classified as a cell-cycle nonspecific antineoplastic agent, DTIC is used in the ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) regimen to treat Hodgkin's lymphoma [21] and is a first-line chemotherapy for metastatic malignant melanomas [22] as well as a therapy for treating soft-tissue sarcomas [23].

The typical method of choice for forming asymmetrical 1-aryl-3,3-dialkyl-triazenes entail long-standing protocols of *N*-coupling between dimethylamine and diazonium salts that have either been previously isolated or generated *in situ* [4]. Nevertheless, there have been a few recent approaches that have taken on a strikingly different nontraditional course [24].

In this context, the thrust of this current investigation is in demonstrating an alternative protocol of modest yet significant variation towards the formation of these useful triazene motifs, by way of an operationally simplistic and mild procedure. *In lieu* of the employment of the commercially available dimethyl amine reagent, *N*,*N*-dimethyl formamide (DMF) provides a source of *in situ* generated nucleophilic dimethyl amine species which subsequently capture the respective diazonium ion, diazenyl radical ($X—C_6H_4N_2\bullet$), or a related entity [25]. The procedure provides modest yields across a spectrum of diazoniums salts, but is currently not fully optimized, being limited to a degree by a competitively formed protodediazoniation reduction product. Nevertheless, the protocol represents a step forward from the one lower yielding literature example described as a side-product from over 20 years ago and that will be subsequently discussed.

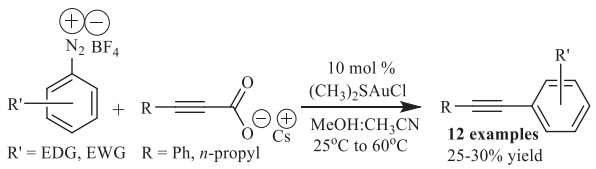
1.1. Background materials and methods

In general, the new procedure encompasses the dropwise addition of a methanolic solution of carbonates or carboxylates to a gently warmed DMF solution of a previously isolated diazonium tetrafluoroborate salt. The reaction is understood to occur through a radical process, as indicated by the results of others, these investigations, as well as the findings from our previously described work.

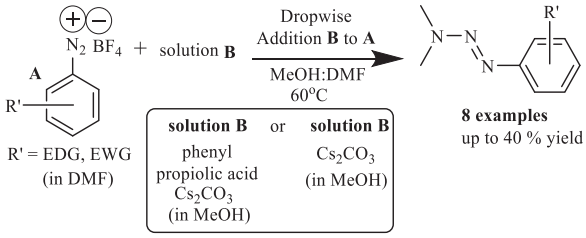
In this realm, we recently investigated a novel gold(I)-catalyzed decarboxylative Sonogashira reaction between isolated aryl diazonium salts and alkynoate (alkanoate) salts performed under mild conditions to produce cross-coupled products (Scheme 2) [26]. (This reaction is subsequently referred to as the original or cross-coupling protocol). The cross-coupling afforded modest yields (20—40%) across an array of functionalized aryl diazonium tetrafluoroborate salts used in their isolated form.

These isolated diazonium salts were generated according to recent literature, by diazotization of the corresponding amines dissolved in methanol through the dropwise addition sequentially of $BF_3{\cdot}OEt_2$ and *t*-butyl nitrite at − 15 °C followed by subsequent warming towards room temperature [27].

Once isolated the requisite diazonium salt was taken up into a DMF/acetonitrile solution and concomitantly conditioned briefly with a simple gold(I) catalyst. Coupling then commenced immediately upon the dropwise addition of a methanolic solution of an alkynoate salt. These alkynoate salts in turn were derived from commercially available phenyl propiolic or 1-hexynoic acid that had been deprotonated with cesium carbonate upon room temperature stirring in methanol for 1 h. The so-called "cesium effect" is presumably leveraged [28], in imparting enhanced dissolution.



Scheme 2. Coupling of Diazonium Salts with Alkynoic Acids Catalyzed by Gold(I).



Scheme 3. Triazenes Generated from Reaction of Diazonium Salts with Carbonate/Carboxylate Salts.

1.2. Current investigational set-up and procedure

With this background in mind, two new-founded protocols will be delineated, including their procedural discoveries and optimization attempts. Advanced in this current investigation these include the dropwise addition of a carboxylate or carbonate, serving as activators, to isolated diazonium salts dissolved in DMF.

In this vein, in trying to ascertain the role of each reagent in our previously developed cross-coupling methodology, the work turned toward running the cross-coupling reaction analogously without the gold(I) catalyst and then subsequently without phenyl propiolic acid as well. Remarkably, there was a notable change in the course of the reaction outcome (Scheme 3).

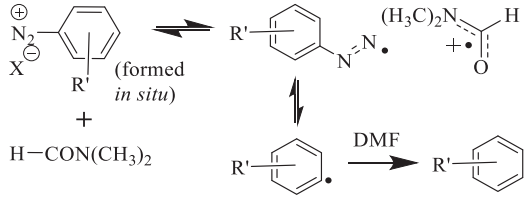
In this regard, addition of solution **B** in both circumstances (either as a methanolic solution of carboxylate or carbonate) to solution **A** (as a DMF solution of diazonium tetrafluoroborate salt) generated a competitively formed dediazoniation reduction byproduct [29] as described in the original protocol. However, instead of concomitant generation of a cross-coupled product, it was discovered that 1-aryl-3,3-dimethyl triazenes were produced appreciably from a similar range of previously employed isolated diazonium salts.

1.3. Comparable background work

Interestingly, these results stand somewhat in contrast with the findings of Doyle et al. [30]. who optimized metal-free reductive aminations in the 1970s. In their seminal work, protodediazoniation (H-atom abstraction) (Scheme 4) transpired from *in situ* generated diazonium salts, which were formed from dropwise addition of various nitrites to arylamines dissolved in DMF.

This solvent presumably serves as the single electron donor source in diazonium salt to diazenyl radical transformations. Additionally, DMF functions as the hydrogen atom source for abstraction by the nascent aryl radical, itself stemming from collapse of diazenyl radical through a β-scission process. Earlier precedent of this fashion employing metal catalysts is notable [31].

On the other hand, two decades after Doyle's findings, Markgraf and others [32] performed a similar reductive substitution on aryldiazonium tetrafluoroborate salts with the distinction of being employed in their isolated form. Although they effectively obtained



Scheme 4. Doyle's DMF-promoted Dediazoniation.

the protodediazoniation products correspondingly, they duly called attention to one side-product which formed, 1-(4-nitrophenyl)-3,3-dimethyltriazene, albeit in low yield via the presumed intermediacy of a 4-nitrophenyldiazenyl radical, with which they give consideration. In this vein, I wish to demonstrate an advancement of Markgraf's preliminary findings towards this triazene motif. Notably, no other body of work appears to exist regarding this kind of approach.

1.4. Experimental results part one: original conditions

Depicted in Table 1 are the diazonium salt to 1-aryl-3,3-dialkyl-triazene conversions that were performed for this current methodology. Based in part upon availability, R′ substituent(s) were employed which elicited variations in electronic effect on the diazonium salt to which they were appended (**1a**–**1h**), as exhibited in entries **1**–**8**.

Reaction runs first employed the addition dropwise of the cesium salt of phenyl propiolic acid **2** to the respective diazonium salts **1a-h**. The isolated yields **3a**-**h** obtained after purification were modest (20–40% in Table 1). Nevertheless they represent the predominant product according to TLC monitoring, although it should be mentioned that the relatively nonpolar dediazonized products on TLC disappear rather quickly.

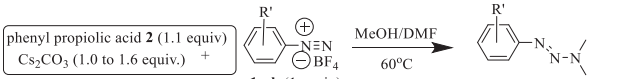
Substituents located at the *para*-position of the benzene ring directly act upon the diazonium reactivity. Therefore, a correlation between stereoelectronics of the substituted diazonium salts and their corresponding triazene product yield (**3a**-**3f** vs **3g**) seems plausible, but is obviously not fully explored.

Interestingly, DMF presents a choice of hydrogen atom abstraction sites. The isolated triazene products **3a**-**g** in addition to product **3h** (Table 1) support formyl H-atom abstraction in which either a formyl radical, or following CO extrusion, a dimethyl amine radical combine with diazenyl radical or related species.

1.5. Further discussion of experimental results

Notice that 1,3-benzodioxole diazene carboxamide product **3h** is distinguished from all the other isolated products **3a**-**g** which are representative 1-aryl-3,3-dialkyl-triazenes. Product **3h** presumably forms from capture of diazenyl radical or related species by a formyl radical before it undertakes extrusion of carbon monoxide. This

Table 1
Triazene generation Examples.



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	**3a**	40[a]	5	**3e**	35[a]
2	**3b**	30 [a]	6	**3f**	25[a]
3	**3c**	35[a]	7	**3g**	20[a]
4	**3d**	30[a]	8	**3h**	20[a]

A: All reported yields are isolated and after chromatographic purification.

product is an interesting one as only the most electron-rich substrate from this investigation furnished this type of product. Interestingly, the loss of CO from an aminoacyl (formamide) radical is not fast which could be an explanation for the low yields overall in this study [33] when pitted against the relatively fast protodediazoniation.

The ^{1}H NMR spectra of the 1-aryl-3,3-dimethyl triazene series exhibit significant line broadening [34] of the *N*-methyl resonances (ca. δ 3.3–3.5 ppm), and highlight differences in chemical exchange line shapes depending on substitution pattern. Restricted rotation around the N2–N3 bond, as described in the introduction, for the zwitterionic resonance form is enhanced by electron withdrawing substituents [35]. The presence of strongly pi-electron withdrawing groups on the aryl ring of the triazene products especially restricts the rotation to the point where the N–Me signals of the rotamers are distinct even at room temperature (**3a-3d**, **3f**). This finding contrasts with examples **3e** and **3g** which exhibit relatively greater pi-electron donation from their appended substituents. Consequently this effect reduces the restricted rotation to the point where these triazene products possess one, albeit broadened, N–Me signal.

The nature of the solvent system, functionality of the diazonium salt, as well as other conditions including reaction atmosphere and reaction pH all can bear influence on the reaction pathway [36], and some of the course effects undertaken for this investigation will be delineated briefly as preliminary findings.

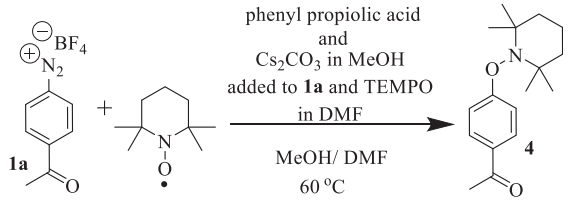
For a given diazonium salt substrate, usually the characteristics of the solvent holds a predominant guiding influence on the nature of the *in situ* generated reactive intermediates. For example, Markgraf has noted that 4-nitrobenzenediazonium tetrafluoroborate generates the aryl radical in DMSO and DMF, but the aryl cation in acetonitrile. In this investigation, the radical pathway has been thought to be functional using DMF as solvent, and especially so for the diazonium salt substrates containing electron withdrawing substituents [37]. As well, radicals are found to be operational, at least in part, in weakly basic solutions [38] containing these species.

Due additionally to experience from our previously described work, it was presumed from the outset of this current investigation that a putative aryl radical generation to be a likely mechanistic scenario during the reaction course. In this view, a simple radical trapping experiment was executed employing the *N*-oxyl radical TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) with methyl ketone diazonium salt **1a** (Scheme 5). Notably, the covalent adduct, a 2,2,6,6-tetramethyl-1-aryloxypiperidine **4**, was obtained as the major radical trapped product [39].

1.6. Experimental results part two: important modifications to investigation

In the final portion of this current investigation, simple modifications were undertaken to further explore the critical components of this triazene reaction (Scheme 6).

Firstly, upon substituting phenyl propiolate (CCPh) for the less



Scheme 5. TEMPO Radical Trapping Experiment.

Carboxyl Species	R' = NO_2	R' = Br	R' = Br, CF_3	R' =$COOCH_3$	R' = OPh
1. R = O^- (Cs_2CO_3)[a]	30%	40%	30%	30%	15%
2. R = CCPh (Ph propiolate)[b]	35%	35%	25%	30%	20%
3. R = Ph (benzoate)[b]	15%	15%			

(all reported yields are isolated after column chromatography)

all reaction stoichiometry used 1 equiv of diazonium salt. **a**: 1 equivalent; **b**: 1.1 equivalents of carboxylic acid with 1.0 to 1.6 equivalents of Cs_2CO_3

Scheme 6. Survey of Alternative Carboxylate And Carbonate Sources for Triazene Formation.

expensive benzoic acid and in keeping all other conditions the same, the target triazene product was still furnished albeit with somewhat diminished isolated yields (reaction series 3) for a few species. The sluggish methanolic dissolution encountered upon charging and reacting benzoic acid with cesium carbonate may be a contributing factor to this result.

The next logical optimization parameter for exploration in this investigation turned to excluding the carboxylate source altogether. Conveniently, upon switching to cesium carbonate alone without any carboxylic acid additive (reaction series 1) the reaction outcome furnished target compounds with isolated yields and purity in a manner consistent to the carboxylate protocol (reaction series 2). For this reaction series 1, partially replacing the DMF used to dissolve the respective diazonium salt with acetonitrile impeded product formation significantly, as tried with a few examples.

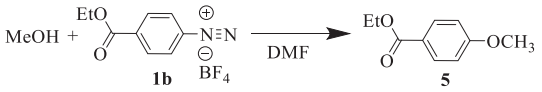
Nevertheless the overarching conclusions drawn from these findings, as exemplified by reaction series 1 conditions, is that this iteration of the methodology is an important one. This is because it reduces to the essentials the reagents needed for the overall reaction, and starts to make this process a potentially viable alternative to dialkyl aryl triazene preparation. A few subsequent reaction conditions were also attempted to continue to investigate the critical parameters.

1.7. Final attempted modifications: other reaction effects and work-up

Firstly, when switching from an inert atmosphere to running a few reactions in air (Scheme 6, series 1 conditions, diazonium salts **1b** and **1c**), TLC monitoring demonstrated fairly clean reaction runs as the triazene and dediazonized product formed in a consistent fashion as with the outgassed method.

With the aim to continue to identify which components are really required, cesium carbonate was also removed from a few of the diazonium salt reaction runs (employing **1b**, **1c** and **1e**), while maintaining all other conditions the same as before. In other words, the reactions were run with dropwise addition of methanol only to a DMF solution containing diazonium salt.

Along with dediazonized product, TLC analysis of reactions from **1c** and **1e** demonstrated a possible triazene product generation. However their isolation remained elusive. In this regard, with no prior work-up, the reaction products were converted almost exclusively into what appeared to be the dediazonized species upon concentration, as observed by TLC. This concentration, which necessitated azeotropic distillation of DMF with toluene, probably negatively impacted the product isolation because of the acidic conditions produced from this reaction course (ca. pH 1 according to litmus paper).



Scheme 7. No Base Added for Methyl Ether Generation from Diazonium Salt **1b**.

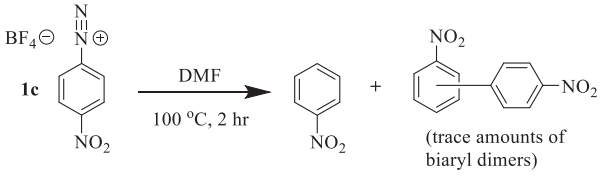
Conversely, upon addition of brine only as part of an extractive workup, followed by concentration and column chromatography, the major product isolated originating from diazonium salt **1b** was aryl methyl ether **5** (Scheme 7). Interestingly, no triazene product was observed by TLC. This notable result is consistent with previous studies in which the thermal decomposition of a diazonium salt in alcoholic solutions yields mixtures of alkyl aryl ethers and reduction products [40]. Furthermore, this specific outcome indicates the importance of the Cs_2CO_3 base in promoting the formation of triazene product. In the absence of buffers the reaction mixture becomes appreciably acidic as the diazonium salt decomposes [41]. This acidity is likely also attributable to DMF decomposition during the reaction course, as will be indicated subsequently in the mechanism section. The developing acidic environment in turn may affect the reaction pathway by transitioning it away from a radical and to a cationic one.

Next, to rule out that DMF could act as the exclusive reagent which lead to the triazenes in this study, Markgraf's preparatory-scale procedure was followed [32]. Accordingly, diazonium salt **1c** was heated in DMF, without any other reagents, to 100 °C for a little over 2 h. Interestingly, GC-MS analysis (ThermoFisher Trace 1310) of the crude reaction, whether performed under argon or in air, demonstrated the main product (Scheme 8) to be the dediazonized species nitrobenzene along with trace amounts of biaryl dimers.

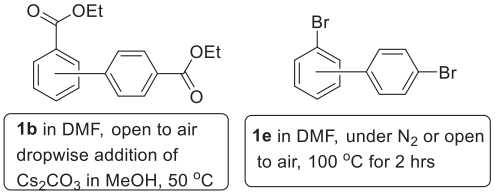
As well, GC-MS analysis of a reaction aliquot stemming from **1e** reflected a comparable result under the Markgraf conditions. The main product is bromobenzene as a result of dediazoniation, as well as trace amounts of biaryl dimers (Scheme 9).

Notably also are biaryl dimer products stemming from aryl ester diazonium salt **1b** under different conditions. These latter three results collectively may lend to the credibility of diazene intermediates (Ar–N=N–H), which are highly sensitive to air [42] even in adventitious amounts as they can decompose to aryl radicals en route to biaryls.

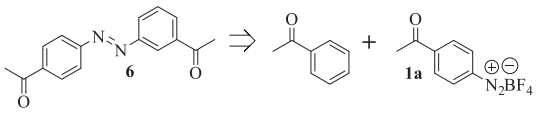
Other reaction outcomes following the Markgraf procedure are noteworthy. Remarkably, while subjecting **1c** to these conditions did not lead to any triazene product, under these same conditions



Scheme 8. Diazonium Salt **1c** Reaction with DMF: Markgraf Conditions.



Scheme 9. Additional Biaryl Dimer Products Observed.



Scheme 10. Azo Compound Side-Product Observed.

1e did lead to a miniscule amount, either under argon or open to the atmosphere. Accordingly, GC-MS analysis of crude reaction runs under air determined the main products to be bromobenzene, 4-bromophenol, two biaryl dimers, and target aryl triazene formed in a 100: 11.4: 5.3: 3:3: 0.24 ratio. While under argon the type and ratio of products remained qualitatively consistent, and quantified to be generated in a 100: 16.5: 7.25: 4.5: 0.37 ratio. Taken another way, following the Markgraf procedure the 4-bromobenzene triazene product was generated in well under 0.5% yield while the 4-nitrobenzene triazene product, which Markgraf had reported in a 10% yield, was not generated at all.

1.8. Brief side-product discussion

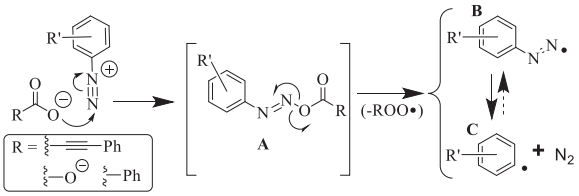
In addition to competitive hydrodediazoniation, another by-product culminating from this current investigation is azo compound **6**, though formed as a relatively minor species (ca. 3–5% yield) for one reaction (using the carboxylate conditions as described in Table 1) and stemming from diazonium salt **1a** (Scheme 10).

It does not appear that azo compound **6** has arisen from direct coupling of arenediazenyl radical due to the observed product regioselectivity. Instead the reaction conditions probably lead to the generation of small amounts of the respective anilines, 4′-aminoacetophenone in this case, along with methyl diazonium intermediates. After subsequent azo coupling directed in a regioselective fashion, the amino group of this aniline could then be removed under the reaction conditions, via triazene formation and isomerization with an unreacted diazonium ion.

1.9. Mechanistic rationale of experimental results

With this background in mind, the remaining focus of this article will be on possible mechanistic rationale for this current study. In this vein, Galli's contemporary and highly informative review on radical reactions of arene diazonium salts [36] serves as a helpful guide in elucidating plausible schemes, under the current investigation's reaction conditions, to account for the generation of the observed triazene products.

To start, depicted in Scheme 11 is a mechanism that is a generally regarded avenue for radical generation resulting from the addition of carbonates or carboxylates to diazonium salts. The resulting labile diazo ether adducts **A** (Ar–N=N–O-R) once formed can fragment homolytically, via their N–O bond, under thermal conditions to generate aryl diazenyl radicals **B**, and thereafter convert into aryl radicals **C** following extrusion of dinitrogen,



Scheme 11. Diazo Ether Adduct Formation and Subsequent Fragmentation.

thereby initiating radical reactions [42].

Diazenyl radicals are reportedly a rare finding in solution. This species type has been established to lose dinitrogen to give the aryl radical with a fragmentation rate constant of ca. 0.4 to 4 × 10^5 s^{-1} [43]. In addition to the diazenyl radical, this thermal fragmentation process generates an alkoxy radical, which in general is not able to undergo subsequent coupling [36].

In addition, to the aryl radicals **C** (Scheme 11) known to be able to abstract a hydrogen atom from the organic solvents [44] usually employed in reduction, such as dimethylformamide, alkoxy radicals have been investigated experimentally and computationally for their ability to do the same. For example, Salamone and coworkers [45] have recently studied the precoordination between alkoxy radicals and DMF computationally, the favorable thermodynamics of the subsequent H-atom abstraction process, in addition to the facile nature of dimethylamine $(CH_3)_2N$ radical generation. In an independent study, the generation of $(CH_3)_2N\bullet$ radicals from DMF has recently been investigated both experimentally and computationally [46], and insights into radical generation from DMF employing mild bases have been generated [47].

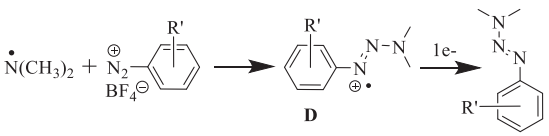
The electrochemical properties of DMF and respective diazonium salts enable a moderately dynamic electron-transfer event between these redox active molecules, though DMF has a higher oxidation potential (greater than 1 V) than other solvents such as simple amines. Nevertheless, DMF in our system appears to be the most suitable electron donor to the diazonium salts employed. As well, the half-wave one-electron reductive potentials of substituted diazonium salts has been elucidated and correlate well [48] to their electron-donating or electron-withdrawing properties of attached substituents.

Irrespective of the substitution pattern, diazonium salts generally have sufficient oxidizing power to enable DMF to serve as the mediator in ET, compared with aryl halides. In support of this current investigation, Galli has noted in his review [36] that carboxylates and alkoxides would not be able to release directly an electron to ArN_2^+. He furthermore points out that the reactivity profile of the homolytic pathway depends upon the interplay of at least four prominent stipulations: the affinity toward the electron of the diazonium substrate, the reducing efficiency of the electron donor, the characteristics of the reaction environment, and the rates of the reactive steps opened to the radical species. As the release of an electron to a diazonium salt may be accomplished in several ways, the following are envisioned as some plausible mechanistic scenarios for generation of the dialkyl triazene product.

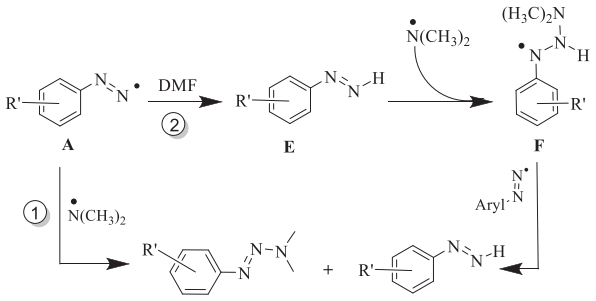
First, as depicted in Scheme 12 is a mechanism giving consideration to the early work in the arena of azoarene formation [49] that cannot be ruled out.

Here the addition of an amine radical to a diazonium salt en route to triazene product via the intermediacy of species **D** is depicted. This mechanism gives consideration to a potential correlation between stereoelectronics of diazonium salts and their corresponding reaction yield, as previously discussed.

On the other hand, outlined in Scheme 13 is a completely different mechanism. First diazenyl radical **A** could be generated directly from the initial diazo ether homolysis as previously



Scheme 12. Triazenes via Electron Transfer.



Scheme 13. Triazenes by way of Diazenes

described (Scheme 11). Then again it could also conceivably be formed by initial transfer of one electron to diazonium salt, possibly from DMF or another source. Once generated, the diazenyl radical **A** could be trapped to form the triazene product in a radical combination event (1).

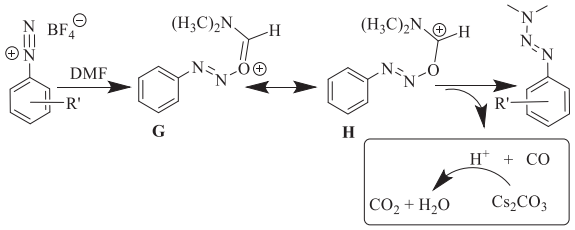
Alternatively, the diazenyl radical could abstract a hydrogen atom from DMF radical cation or DMF. The resulting aryl diazene **E** could react subsequently with a dimethyl amine radical to generate a hydrazinyl radical **F** [50]. This species could then be oxidized via a hydrogen atom abstraction [51] to form the triazene product (2). This pathway was investigated to a small extent as previously described by changing the access of the reaction to air, as diazenes are known to be highly sensitive to oxygen.

Finally as displayed in the following two schemes, an inner-sphere and/or outer-sphere electron transfer mechanism is plausible as outlined in previous work on hydrodediazoniation [32,52]. The inner-sphere electron transfer process is the more likely of the two possibilities to account for triazene product generation. Nevertheless, both will be given consideration for this current investigation.

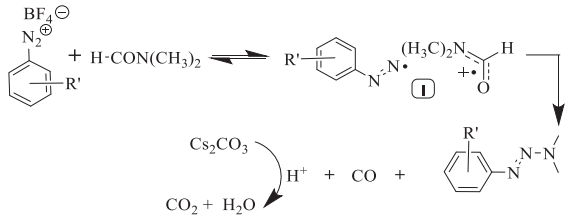
Accordingly in Scheme 14, an inner-sphere electron transfer (ET) may transpire en route to triazene formation, via the intermediacy of covalent diazo ether adduct **G**/**H**. This adduct could subsequently undergo collapse by way of a 1,3-rearrangement to the triazene in a concerted four-centered reaction event [53].

The inner-sphere ET is known as a bonded electron transfer process. This is because it proceeds from a covalent linkage (in this case between diazonium salt and DMF) as the participating sites have become connected by a chemical bridge. This concerted mechanism is considered the most likely to be occurring by Markgraf [32].

On the other hand, if an outer-sphere dissociative ET is operative, as is displayed in Scheme 15, then the chemical species in effect remain separate and intact before, during, and after the ET event. In this manner and occurring in a step-wise fashion, an intimate cation radical pair **I** is formed from direct reduction of diazonium salt by DMF. Coupling can then plausibly occur within the solvent cage to form triazene adduct.



Scheme 14. Triazenes via Inner-Sphere ET.



Scheme 15. Triazenes via Outer-Sphere ET.

This scenario is regarded as being the most likely in Doyle's DMF promoted hydrodediazoniation of *in situ* generated diazonium salts [30].

As the release concomitantly of CO and H^+ occurs regardless of the electron transfer mechanism (Scheme 14 or Scheme 15), cesium carbonate in this current investigation's reaction system seems to serve a critical role as buffer against developing reaction acidity. As well, the reaction progress may be facilitated in part by conversion of the generated carbonic acid, formed during this neutralization, into water and CO_2, which according to Le Chatelier's Principle drives the reaction towards completion. This may account for the significantly reduced requirement of working reaction temperature, observable even between 25 and 30 °C, when compared with Markgraf's investigation [32]. The cesium carbonate may furthermore play an influential role in dictating the nature of intermediates in play, as diazonium chemistry is known to be sensitive to reaction pH as previously described [36].

1.10. Work most closely resembling this methodology

The working conditions of Markgraf et al. [32]. most closely resemble those employed in this current investigation. Markgraf also utilized an isolated diazonium tetrafluoroborate salt that was dissolved in DMF. His work however required high heating of up to 100 °C over a 2 h period en route to mainly protodediazonized product along with a sparing amount of one triazene product, observed apparently in about 10% yield. No other procedure that I am aware of stipulates a triazene product generation via a method of this nature. Clearly the diazonium salt activation in this current study, by dropwise addition of carbonates or carboxylates, is an important feature change that has enabled reactions to take place even at room temperature. Complete consumption of diazonium salt occurs within minutes.

2. Conclusion

In conclusion, the addition of methanolic solutions of carbonates or carboxylates to shelf stable isolated diazonium tetrafluoroborate salts dissolved in DMF has enabled the preparation of a variety of triazene derivatives under mild and operationally straightforward conditions. From a microscopic perspective, this chemical transformation harnesses the potential energy of diazonium salt starting materials by producing relatively more stable aryl dialkyl triazene products [3b,54] under mild conditions. Furthermore the accompaniment of the irreversible loss of gaseous species facilitates the reaction progress. This modified methodology for the generation of 1-aryl-3,3-dialkyl-triazenes has been accomplished by way of *in situ* generated dimethyl amine radicals (or related species) originating from DMF and their subsequent coupling with isolated diazonium salts **1**. Activation appears to embark only once the dropwise addition of the carbonate/carboxylate species to the diazonium salt commences [55]. In this regard, visual reaction progress analysis demonstrates an immediate onset of reactivity within several seconds marked by gas evolution and reaction darkening. The gas bubbling does not subside until after the carbonate/carboxylate addition has completed. As well, according to TLC analysis there is unnoticeable reaction conversion after the completion of this addition. The reaction does not appear to be intolerant to oxygen.

Continued investigation of the generality of this methodology and its refinement together with the unraveling of the critical mechanistic details of this process may enable its application towards triazenes that present synthetic challenges, and pave the way for this methodology's application in related transformations as well.

2.1. Cautionary statements

Diazonium salt handling in the laboratory requires precautionary measures [3b,56] because these species are heat and shock sensitive. Nevertheless, the tetrafluoroborate counterions usually impart sufficient stability to render acceptability to all of the non-heterocyclic aromatic compounds [57] that have been used in this and our previous work [26].

2.2. General procedure

The reaction setup does not require any elaborate manipulations, and all materials are sufficiently handled. This reaction procedure first involves the generation of a homogeneous methanolic solution of cesium phenyl propiolate salt or simply a methanolic solution of cesium carbonate. In either case cesium carbonate is quickly charged into a round bottom flask under Schlenk conditions due to its modest hygroscopic nature and either combined with phenyl propiolic acid or left as is before addition of methanol. In both circumstances the methanolic mixture reaches complete dissolution after a period of about 1 h at room temperature. Next, dropwise addition of this newly generated homogeneous ca. 0.2 M anhydrous methanolic solution to a ca. 0.2 M anhydrous DMF solution of diazonium salt that had been heated to 50–60 °C occurs over the course of several minutes. Gas evolution is noted, as indicated by some reaction bubbling, eventually subsiding after the dropwise addition is completed. Nevertheless subsequent stirring at this temperature commences for a period of a few hours, akin to the work of Doyle. As another indicator of reaction progress, the reaction darkens significantly during the time course of the dropwise addition, turning from usually a pale yellow color initially to a reddish hue, and then to a very dark purple tone.

Likewise, the reaction workup is performed in a simple fashion by first adding a small portion of Amberlyst 15 DRY to the crude mixture until affording a mildly acidic pH (ca. 6) as observed by litmus paper. Second, gravity or vacuum filtration is performed to remove spent ion exchange resins. Finally, crude product isolation is completed via rotovap concentration. Residual DMF is removed via azeotropic distillation with small amounts of added toluene. The concentrated crude products are then subjected to flash chromatographic separation under gradient mobile solution conditions (straight hexanes followed by 0.5% and usually up to 3% ethyl acetate in hexanes) to provide a modest isolated yield of triazene products (20–40%).

2.3. Detailed experimental procedure

An actual procedure follows. A homogeneous methanolic solution is created by combining cesium carbonate (391 mg, 1.21 mmol, 1.6 equivalents) with phenyl propiolic acid (109 mg, 0.75 mmol, 1.0 equivalents) with complete dissolution occurring over a 1-h period. (Here as well, many successful procedures used just a slight excess

of cesium carbonate relative to the phenyl propiolic acid). If cesium carbonate is used alone, then its stoichiometric ratio is kept to ca. 1.05 equivalents relative to the diazonium salt substrate. Either way, this solution is next added dropwise to a DMF solution of diazonium salt bromide **1e** (202 mg, 0.75 mmol, 1.0 equivalents), with stirring around 60 °C. A darkening of the reaction solution and bubbling is noted during this addition process. TLC monitoring of the reaction after several minutes shows the reaction progress to be near completion. The reaction is stopped after a few hours and worked up with a small portion of Amberlyst Dry, filtered, and concentrated under vacuum. Column chromatography (0.5% ethyl acetate in hexanes up to 3% ethyl acetate in hexanes) furnishes the product. In addition to the target product, the relatively less polar dediazonized product is visible on TLC and often disappears due to volatility. As well, a highly polar and brightly colored resinous compound with poor solubility and ambiguous NMR is observed, as reported in Doyle's previous work [30].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132185.

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