Alkynyl triazenes enable divergent syntheses of 2-pyrones‡

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The 2-pyrene motif occurs frequently in bioactive natural products and is appreciated as synthetic intermediates. However, only few methods allow for diversifying functional group modifications on this relevant heterocycle. The distinct properties of 1-alkynyl triazenes promote a smooth addition of propiolic acids across the triple bond. Addition of catalytic amounts of silver salt induces cyclization to 2-pyrones. Depending on the reaction temperature, either 6-triazenyl or 5-triazenyl 2-pyrones are selectively formed. The triazeny unit is subsequently replaced by a variety of valuable groups in a one-pot process yielding for instance 2-fluoro pyrones. The substitution occurs with an intriguing 1,5-carbonyl transposition. Moreover, the triazeny group serves as traceless activating group for subsequent Diels–Alder cycloadditions and as a constituting unit for rare fused aminopyrazole pyrone heterocycles.

Introduction

2-Pyrones represent a frequently encountered framework in diverse bioactive natural products, exhibiting a broad range of antifungal, antibiotic, cytotoxic and phytotoxic activities (Fig. 1). These occurrences and properties sparked interests in the scaffold and motivated the development of 2-pyrene syntheses. To date, the repertoire of synthetic methods to access 2-pyrones include cyclizations, ring expansions, cyclo-trimerizations and transition metal-catalyzed vinylc C–H annihilations. However, despite these diverse strategies, the reachable functional group variability on 2-pyrones remains relatively limited compared to that of the related benzanulated congeners, the isocoumarins. For instance, reported substituents at the 6-position are largely restricted to aryl or alkyl groups, while halo or other heteroatom substituents are scarce (Fig. 2a). This might be attributed to tedious or non-viable routes to elaborate starting materials required for their construction. The limited substituent flexibility constitutes a bottleneck for medicinal chemistry studies involving these heterocycles.

Besides their bioactive properties, 2-pyrones are attractive dienes in Diels–Alder reactions delivering highly elaborate arenes after expulsion of CO2. However, installations of additional electron-donating substituents such as amino or methoxymethyl groups are often required to enhance their reactivity (Fig. 2b). Subsequent removal of these substituents, or difficulties in subjecting them to functional group manipulations, render the normal electron-demand Diels–Alder reaction of 2-pyrones far less adopted in total synthesis than its inverse electron-demand counterpart.

Over the past years, the use of alkynyl triazenes has gained momentum in organic synthesis. They possess a unique ynamide-like reactivity, and are compatible with transition metals paired with versatile transformability into numerous functional groups. These values drew our interest to access triazeny pyrones, which would in turn enable a divergent access to various functionalized pyrones. Inspired by Cui’s synthesis of 2-pyrones from ynamides (Fig. 2c), we hereby report a smooth addition of propiolic acids to alkynyl triazenes, followed by a silver-catalyzed cyclization to triazeny 2-pyrones (Fig. 2d). Divergent elaboration of the triazeny groups into various valuable groups occurs under an unusual 1,5-carbonyl transposition delivering 3,4-substituted isomers. The triazeny unit also serves as a traceless activating group for subsequent Diels–Alder reactions delivering highly elaborate arenes after expulsion of CO2. Furthermore, installations of additional electron-donating substituents such as amino or methoxymethyl groups are often required to enhance their reactivity (Fig. 2b). Subsequent removal of these substituents, or difficulties in subjecting them to functional group manipulations, render the normal electron-demand Diels–Alder reaction of 2-pyrones far less adopted in total synthesis than its inverse electron-demand counterpart.

The 2-pyrene motif occurs frequently in bioactive natural products and is appreciated as synthetic intermediates. However, only few methods allow for diversifying functional group modifications on this relevant heterocycle. The distinct properties of 1-alkynyl triazenes promote a smooth addition of propiolic acids across the triple bond. Addition of catalytic amounts of silver salt induces cyclization to 2-pyrones. Depending on the reaction temperature, either 6-triazenyl or 5-triazenyl 2-pyrones are selectively formed. The triazeny unit is subsequently replaced by a variety of valuable groups in a one-pot process yielding for instance 2-fluoro pyrones. The substitution occurs with an intriguing 1,5-carbonyl transposition. Moreover, the triazeny group serves as traceless activating group for subsequent Diels–Alder cycloadditions and as a constituting unit for rare fused aminopyrazole pyrone heterocycles.

Fig. 1 Bioactive 2-pyrene containing natural products.
Alder cycloadditions and as a constituting unit for fused aminopyrazoles.

**Results and discussion**

Our studies were initiated by investigating the reaction between phenyl propiolic acid (1a) and alkynyl triazene 2a (Table 1). At 60 °C in toluene, addition of 1a to 2a formed acyloxy alkene 3aa in 95% yield and complete regioselectivity (entry 1). The sequential addition of catalytic AgSbF$_6$ initiated cyclization to 6-triazynyl pyrone 4aa along with minor amounts of isomer 4aa’ (entry 2). The structure of 4aa was confirmed by X-ray crystallography.$^{16}$ 4aa’ is presumably formed from the thermodynamic regioisomer 3aa’. Indeed, a 1 : 1 mixture of 3aa and 3aa’ was observed at 100 °C in the absence of AgSbF$_6$ (entry 3). Performing the process at ambient temperature in CH$_2$Cl$_2$ led to quantitative and exclusive formation of 4aa (entries 4–6). The direct addition of AgSbF$_6$ at the start of reaction, or using a 5 mol% loading, resulted in lower yields (entries 7 and 8). Very notably, conducting the reaction at 100 °C strongly favored the formation of isomer 4aa’ in good yields (entries 10–12). In summary, this is a simple temperature switch of the reaction outcome.

Despite the highly-valued fluorine effect in heterocycles in drug discovery,$^{17}$ fluorinated 2-pyrones remain the rarest and least reported among functionalized 2-pyrones.$^{18}$ The complete lack of suitable methods to access 6-fluoro 2-pyrones underscores the formidable challenges of regioselective fluorination of 2-pyrones. To address this gap in synthetic methodology, we opted to transform the triazene unit into a multi-leveraging activity and selectivity handle for the 2-pyrene synthesis and functionalization.

### Table 1 Optimization studies of the triazynyl pyrone formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (3aa : 3aa’)</th>
<th>% yield 3aa</th>
<th>% yield 4aa</th>
<th>% yield 4aa’</th>
<th>4aa : 4aa’</th>
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<tbody>
<tr>
<td>1</td>
<td>60 PhMe</td>
<td>95 (&gt;20 : 1)</td>
<td>Trace</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>60 PhMe</td>
<td>75</td>
<td>8</td>
<td>10 : 1</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>100 PhMe</td>
<td>46 (1 : 1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>23 PhMe</td>
<td>92</td>
<td>—</td>
<td>&gt;20 : 1</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>23 CH$_2$Cl$_2$</td>
<td>99</td>
<td>—</td>
<td>&gt;20 : 1</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>23 CH$_2$Cl$_2$</td>
<td>98$^*$</td>
<td>—</td>
<td>&gt;20 : 1</td>
<td>—</td>
</tr>
<tr>
<td>7$^a$</td>
<td>23 CH$_2$Cl$_2$ 38 (&gt;20 : 1)$^b$</td>
<td>49</td>
<td>—</td>
<td>&gt;20 : 1</td>
<td>—</td>
</tr>
<tr>
<td>8$^a$</td>
<td>23 CH$_2$Cl$_2$</td>
<td>68</td>
<td>—</td>
<td>&gt;20 : 1</td>
<td>—</td>
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<tr>
<td>9</td>
<td>100 PhMe</td>
<td>13</td>
<td>58</td>
<td>1 : 4.5</td>
<td>—</td>
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<tr>
<td>10$^b$</td>
<td>100 PhMe</td>
<td>12</td>
<td>72$^b$</td>
<td>1 : 6</td>
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</tr>
<tr>
<td>11$^b$</td>
<td>100 PhMe</td>
<td>13</td>
<td>65</td>
<td>1 : 5</td>
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<tr>
<td>12$^b$</td>
<td>120 PhMe</td>
<td>13</td>
<td>70</td>
<td>1 : 5.4</td>
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*Conditions: (i) 0.11 mmol 1a, 0.10 mmol 2a, 0.2 M in the indicated solvent and temperature for 12 h, (ii) 10 μmol AgSbF$_6$, 12 h, yield and ratio determined by 1H-NMR with an internal standard.$^{19}$ 12 h for (ii), no AgSbF$_6$. $^a$ (i) 0.11 mmol 1a, 0.10 mmol 2a in CH$_2$Cl$_2$ for 2 h, (ii) 10 μmol AgSbF$_6$, 23 °C for 1 h. $^b$ 0.11 mmol 1a, 0.10 mmol 2a, 10 μmol AgSbF$_6$ in CH$_2$Cl$_2$ at 23 °C for 24 h. $^c$ 5 μmol AgSbF$_6$. $^d$ With 0.15 mmol 1a.$^e$ With 0.18 mmol 1a.$^f$ Isolated yields. Ortep structure of 4aa with thermal ellipsoids are at 50% probability. Hydrogen atoms are omitted for clarity.
and complete 1,5-transposition. 1-Naphthyl- (5ia) and a thiényl-substituted products (5ja) were as well accessed. Alkyl groups like cyclopropyl (5ka) and propyl (5la) were well accepted. The use of parent propionic acid 1m provided 3-phenyl-6-fluoropyrone 5ma. Concerning the alkynyl triazenes, various aryl and alkyl substituents consistently reacted well and afforded pyrones in good yields and full regioselectivity (5ab–5ai). X-Ray crystallographic analysis of 5da and 5ac confirmed assignment of the substituent R1 and R2 on the pyrone core.16 During our investigations, very notable reactivity profiles were encountered with specific alkynyl triazenes. In particular, cyclopropyl-substituted substrate 2g provided pyrone-fused N-aminopyrazole 6ag in 76% yield whereas the expected fluoro- pyrone was not observed at all (Scheme 3).19 This highly rare fused double heterocyclic system was as well obtained with tethered 1-diynyl triazene 2h. The structures of 6ag and 6ah were unambiguously confirmed by single crystal X-ray diffraction. We reasoned that the N-aminopyrazoles arose from triazyl pyrone intermediates 4ag and 4ah via the depicted mechanisms.20 For 4ag, a cyclopropane ring opening assisted by triazene or the conjugated oxygen leads to X and Y. An intramolecular cyclization and a subsequent rearomatization then give rise to 6ag. In a similar fashion, displacement of the tosylamido group in 4ah leads to 6ah, further evidenced by the isolation of tosylamide 7. These unique products underscore once again triazenes possess an untapped potential to forge novel and complex fused heterocyclic systems.

Next, we investigated further one-pot divergent functionalizations of the triazyl pyrones (Scheme 4). For instance, performing the one-pot process with 1a and 2a, chloro- (8b), bromo- (9) and iodo-pyrones (10) were efficiently prepared in high yields using the corresponding trimethylsilyl halides. Again, the 1,5-carbonyl transposition was observed for these products. The use of MeOH as the nucleophile gave a 4:1 mixture of transposed dimethoxy orthoester 11 and its non-transposed isomer 11’. Notably, triazyl pyrones engage in normal-electron demand Diels–Alder reactions. For instance, its reaction with acetylene dicarboxylate tetrasubstituted gave arene 12. The triazyl group was cleaved after the cycloaddition, presumably by a thermally-induced radical mechanism,21 as evidenced by some amounts of triazyl arene 13. Anthraquinone 14 was furnished in 69% yield after two consecutive cycloadditions on p-quinone were engaged, followed by triazyl elimination. The use of a larger excess p-quinone gave naphthoquinone 15. Remarkably, the triazene was cleaved cleanly in all Diels–Alder examples. Contrasting to conventional strategies to activate pyrones for Diels–Alder cycloadditions, the triazyl pyrones offer a highly efficient alternative to access densely substituted arenes leveraging the triazene moiety as a traceless activating group.

To the best of our knowledge, the observed pyrone 1,5-carbonyl transposition has not been reported to date. Three plausible pathway for this transposition can be envisioned (Scheme 5).22–24 Initial protonation of the carbonyl oxygen atom may be stabilized by its pyrylium D. For pathway I, a subsequent nucleophile addition leads to B. In turn, B eventually undergoes a oxa 6π-electrocyclic ring opening25 leading to 4-hydroxy unsaturated acyl triazene C. Lactonization of the activated acyl triazene unit24 delivers transposed product 5. For pathway II, the hydroxy group of A alternatively might undergo a substitution by the nucleophile generating cationic intermediate D and a molecule of water. Species D may be stabilized by its pyrylium mesomer E. Both are capable of providing 5 upon triazene.
displacement by re-addition of the previously expelled water. A third pathway involves trapping of the putative cation F by an external water molecule to give isomeric hydroxy-pyrones G and H. However, the non-transposed isomer was not observed with any halide nucleophiles. The insufficient discrimination

Scheme 3  N-Aminopyrazole formation from 2g or 2h. Condition: (i) 0.11 mmol 1a, 0.10 mmol 2a in CH₂Cl₂ (0.2 M) at 23 °C for 2 h, (ii) 10 µmol AgSbF₆ at 23 °C for 1 h, (iii) 1.0 mL HF-py at 60 °C for 3 h.

Scheme 4  One-pot divergent formation of functionalized 2-pyrones and engagement in Diels–Alder cycloadditions. Condition A: 0.11 mmol 1a, 0.10 mmol 2a, 0.2 M CH₂Cl₂ at 23 °C for 2 h, then 10 µmol AgSbF₆ at 23 °C for 1 h.
between G and H reduces the likelihood of pathway III. Similarly, pathway II has a lower possibility as A should also be capable of generating the non-transposed isomer with halides.

Experimentally, isotope spiking experiments with 50 equivalents of H$^{18}$O on the fluorination and methoxymethylation did not provide any incorporation of $^{18}$O in 5aa and 11 based on $^{13}$C NMR and mass spectrometry (Scheme 6). This is hinting towards an intramolecular mechanism. Therefore, illustrated pathway I might be the most plausible mechanism for the transposition. Minor isomer 11' would be generated from A using methanol as a nucleophile.

Conclusions

In summary, we reported a one-pot divergent formation of a broad range of functionalized 2-pyrones by leveraging the reactivity of alkyne triazenes on several instances. They first facilitate the addition of carboxylic acids across the alkyne triple bond. Secondly, it can be easily converted into a wide range of desirable functionalities. These comprise the synthesis of unreported 6-fluoro-2-pyrone, as well as pyrones with chloride, bromide, iodide and methoxy substituents at the 6-position. Notably, we have unraveled an unusual and mechanistically intriguing 1,3-carbonyl transposition, evidencing the non-innocent behavior of the triazyl group. Furthermore, the triazyl unit can be used to access rare pyrone-fused pyrazole heterocycles. Moreover, the triazene substituent acts as a traceless activating group facilitating normal electron-demand Diels-Alder cycloadditions, affording densely substituted arene products.

Data availability

The datasets supporting this article have been uploaded as part of the supplementary material. Crystallographic data for 4aa, 5aa, 5ca, 5ac, 6ag, 6ah and 8 has been deposited at the CCDC under 2075639 and 2075641-2075646 and can be obtained from www.ccdc.cam.ac.uk.

Author contributions

JFT, KS and NC conceived, designed and directed the project. JFT conducted the experiments. CTB synthesized the alkyne triazenes. All authors wrote the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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Notes and references


16 Supplementary crystallographic data of the following compounds can be found from The Cambridge Crystallographic Data Centre: 2075639 (4aa), 2075641 (5aa), 2075642 (5ca), 2075643 (5ac), 2075644 (6ag), 2075645 (6ah) and 2075646 (8).


