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# The sequel to a carbocyclic nucleoside synthesis: a divergent access to both arenediazonium ions and aryl triflates

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In memoriam, this Letter is dedicated to Dr. Patrick Léon, who passed away while this work was in progress

**Abstract**—Depending on the amount of acid used, treating aryl–dialkyl triazenes of general structure **3** with triflic acid resulted in the formation of either the corresponding arenediazonium triflates **4** or aryl triflates **8** apparently by two different pathways, the latter conversion being favoured at high acid concentration.


As part of work aimed at synthesising **1a**, a carbocyclic adenosine derivative with promising cardioprotective and antilipolytic properties,[1] we faced the problem of converting aristeromycin **1b** into a corresponding six-halo compound. Since **1b** is accessible by fermentation,[2] successful halo-deamination would have paved the way for a straightforward access to **1a** (Scheme 1).

As anticipated from results obtained with nucleosides,[3] the use of classical, aqueous, Gatterman–Sandmeyer conditions proved ineffective. Better results were obtained by submitting the protected derivative **1c** to aprotic Sandmeyer conditions.

Reacting **1c** with *i*-amyl nitrite and $CuCl_2$ in acetonitrile[4a] was unsuitable, as very stable complexes of the chloride **1d** thus formed with the copper species were produced. The situation was improved by the use of $CCl_4$ as halogen donor,[4b,c] the pure chloride **1d** being then isolated in moderate yield (37%). Finally, treating **1c** with excess *i*-amyl nitrite in hot $CH_2I_2$, with the addition of iodine,[4d] afforded the iodide **1e** in a satisfying 66% yield after purification.[5] Subsequently, condensation of **1e** with the amine **2** in EtOH and in the presence of Hünig's base followed by sequential treatment of the resulting substitution product with TBAF, MeI/*t*-BuOK and concd HCl afforded compound **1a**, with spectroscopic data corresponding to those in the literature.[1,6]

Due to the limited solubility in halogenated solvents of all the compounds in this series, the purification of crude **1e** by column chromatography and re-crystallisation to eliminate by-product hydroxy compounds was rather tedious. With the aim of improving this halogenation step, conversion of **1c** into a triazene derivative was considered.

It has been reported that adding triflic acid (TfOH) to a benzene solution of the triazene **3a** results in the precipitation of *p*-tolyldiazonium triflate **4a** as a crystalline solid.[7] Our hope was that diazotising **1c** and then adding a lipophilic secondary amine to the resulting mixture would furnish a triazene having an appreciable solubility in organic solvents. In the event, treatment with TfOH as above would deliver the corresponding diazonium triflate.[8]

Unexpectedly, reacting **1c** with *i*-amyl nitrite and TMSCl, followed by *N*,*N*-dibenzylamine afforded in low yield (7%) a coloured pasty solid to which the structure **1f** was tentatively assigned (NMR). Moreover, treatment of this product with TfOH failed to give a diazonium derivative and therefore this approach was abandoned.

*Keywords*: Carbocyclic nucleosides; Diazotisation; Diazonium triflate; Triazene; Aryl triflate; Diazo coupling.
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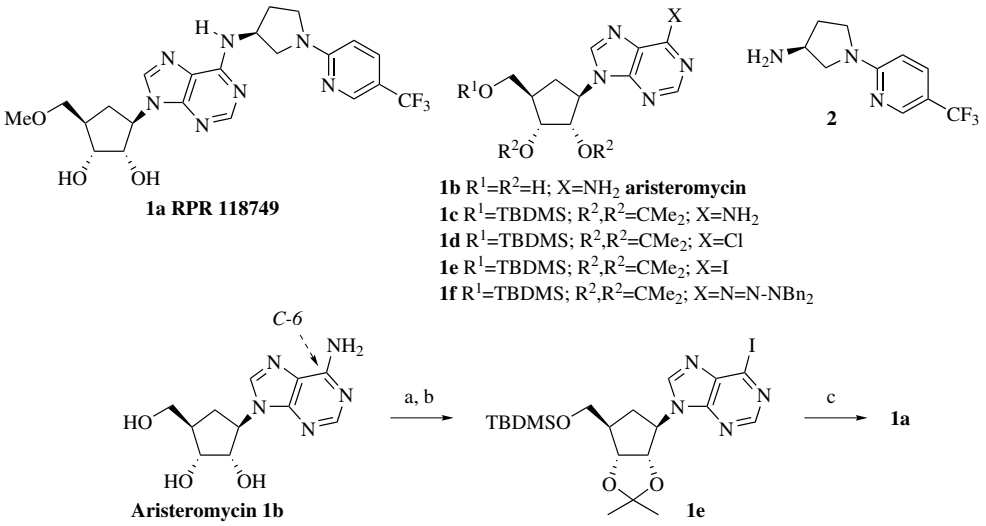



**Scheme 1.** Reagents and conditions: (a) (i) 2,2-Dimethoxypropane (2 equiv), $MeSO_3H$ (1 equiv), acetone (8 mL/mmol); −10 °C to rt, 14 h (85%); (ii) TBDMSCl (1.5 equiv), imidazole (3 equiv), DMF (1 mL/mmol); rt, 15 h (86%); (b) *i*-amyl nitrite (19 equiv), KI (3.3 equiv), $I_2$ (3 equiv), $CH_2I_2$ (6 mL/mmol); 85 °C, 3 h, then 0.25 M (in $CH_2I_2$) *i*-amyl nitrite (13 equiv), 85 °C, 2.5 h (66%); (c) (i) **2** (1.2 equiv), Hünig's base (3 equiv), EtOH (5 mL/mmol); reflux, 1 d (75%); (ii) 1 M (in THF) TBAF·$3H_2O$ (1.1 equiv); rt, 4 h (87%); (iii) *t*-BuOK (1 equiv), methyl triflate (1 equiv) THF (3 mL/mmol); −78 °C, 1.5 h, then *t*-BuOK (0.5 equiv), methyl triflate (0.5 equiv), −78 °C, 1 h (59%); (iv) 37% HCl (7 equiv), MeOH (30 mL/mmol); rt, 5 h (79%).

Our interest then returned to the aforementioned **3a**–**4a** conversion. Unlike more commonly encountered diazonium salts,[9] no general procedure for preparing arenediazonium triflates from triazenes has been disclosed to date. This prompted us to re-examine this result and to this end a series of triazenes was prepared (Scheme 2).

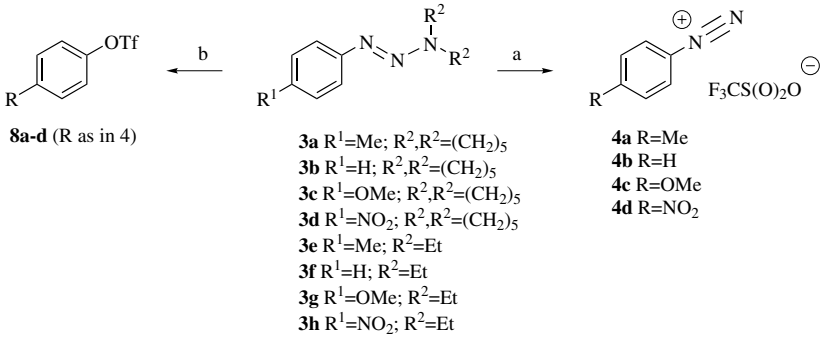
First, the triazene **3a** was reacted with triflic acid in benzene to give a solid, which was filtered and washed with ether as described in the literature.[7] In contrast to that reported in this otherwise valuable publication, NMR examination of this product clearly indicated it to be a mixture of the triflate **4a** and piperidinium triflate. Repeated re-crystallisation of this compound from an acetone/ether mixture provided pure (NMR) **4a** as white needles (10%) with a mp of 81 °C, close to the value obtained by preparing **4a** via a more conventional procedure (ca. 82 °C),[10b] but differing significantly from that reported in Ref. 7 (65 °C), undoubtedly the result of contamination of **4a** by the accompanying piperidinium triflate. Consistently, similar treatment of the parent bisethyltriazene **3e** with TfOH resulted in the separation of an oil, which by trituration in ether afforded crystals identified as *N*,*N*-diethylammonium triflate (NMR).

After extensive experimentation, we found that slowly adding TfOH (2 equiv) to a cold AcOEt (or $CH_2Cl_2$) solution of **3a** then diluting the reaction mixture with ether resulted in the precipitation of pure (NMR) **4a**, subsequently isolated in fair yield (47%) after re-crystallisation.[11a] Comparable results were obtained with triazenes **3b**–**d** (Table 1).

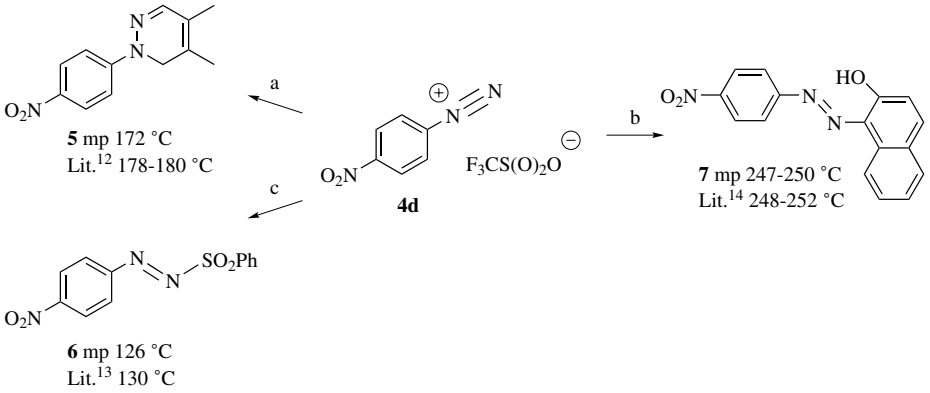
**Table 1.** Conversion of triazenes into arenediazonium triflates[11a]

| Triazene | Solvent | Product (%),[a] mp °C (lit.) |
|---|---|---|
| **3a** | AcOEt | **4a** (47), 81 (82)[10b] |
| **3b** | AcOEt | **4b** (49), 85 (85)[10a] |
| **3c** | AcOEt | **4c** (60), 55 |
| **3d** | $CH_2Cl_2$ | **4d** (85), 99 |

[a] After re-crystallisation from an acetone/ether mixture.




**Scheme 2.** Reagents and conditions:[11] (a) TfOH (2 equiv), AcOEt (or $CH_2Cl_2$; 8 mL/mmol); −15 °C, 5 min, then ether, −10 °C, 2–5 h; (b) TfOH (13 equiv); −10 °C, 2.5 h, then rt, overnight.




**Scheme 3.** Reagents and conditions: (a) 2,3-dimethyl-1,3-butadiene (2 equiv), $CH_3CN$ (1.5 mL/mmol); rt, 10 min (32%, after re-crystallisation); (b) *O*-TMS-β-naphthol (1 equiv), $CH_2Cl_2$; rt, 10 min (quantitative); (c) sodium benzenesulfinate (1 equiv), $CH_2Cl_2$; rt, 1 d (92%).

As observed with the parent fluoroborate (or hexafluorophosphate),[12] reacting **4d** with 2,3-dimethyl-1,3-butadiene afforded the diazine **5** (Scheme 3). Furthermore, adding sodium benzenesulfinate to a solution of **4d** in $CH_2Cl_2$ resulted in the immediate precipitation of the known diazosulfone **6**,[13] thus confirming the strong similarity of arenediazonium triflates with more commonly encountered 'stable' arenediazonium salts. Interestingly, mixing **4d** with the *O*-TMS derivative of β-naphthol in $CH_2Cl_2$ instantaneously resulted in the quantitative formation of a red solid identified as **7** (mp, NMR).[14,15]

Aware of reports of the formation of aryl triflate by-products by treatment of various aryl-*N*,*N*-dimethyl triazenes with CsF in the presence of TfOH,[16] glc analysis of the mother liquors left after crystallisation of **4a** revealed the presence of **8a** (6–18%). These by-products were particularly prevalent in the preliminary experiments conducted with excess triflic acid.

Aryl triflates are also formed by treatment of arenediazonium fluoroborates (or *o*-benzenesulfonimides) with TfOH,[17a,b] a related result being observed by reacting phenyl diazonium fluoroborate with TMS triflate.[17c] In each case either heating, irradiation (mercury lamp) or ultrasonication proved necessary to bring these solvolysis processes to completion. Indeed, heating **4a** at 90 °C in triflic acid for a few hours gave, after hydrolysis, **8a** in acceptable yield (43%).

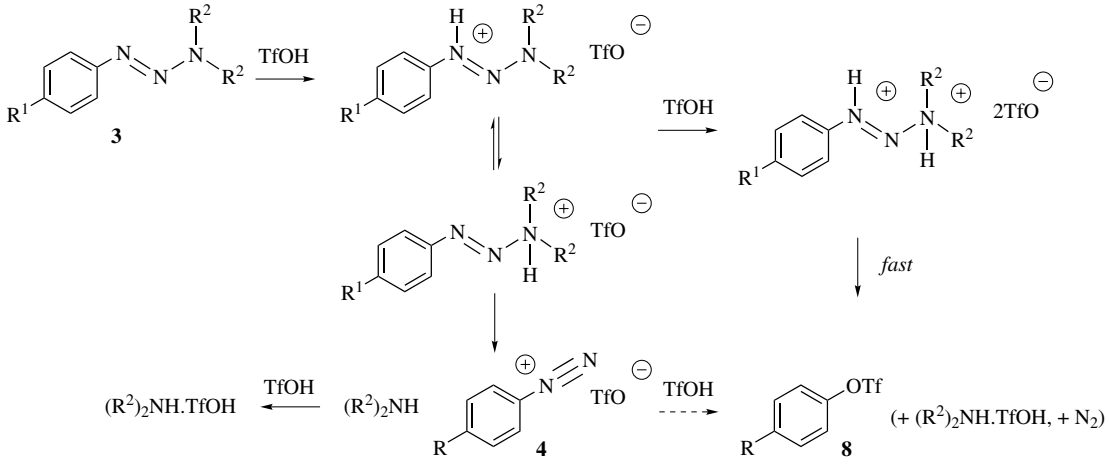
Surprisingly however, **4a** reacted only very slowly when stirred in pure TfOH at room temperature and only trace amounts of **8a** were detected after three hours under these conditions; a similar result being observed with added piperidinium triflate. Thus it was not clear why **8a** was so easily produced during the **3a**–**4a** conversion since all these experiments were conducted in the cold and, moreover, at low acid concentration.

A reasonable explanation came to light when we noticed that adding **3a** slowly to cold, excess (molar ratio 1/13), TfOH resulted in the rapid formation of *p*-tolyl triflate

**Table 2.** Conversion of triazenes into aryl triflates[11b]

| Triazene | Product (%), bp °C (τ)/mp °C |
|---|---|
| **3e** | **8a** (51), 110 (19) |
| **3f** | **8b** (66), 90 (17) |
| **3g** | [a] |
| **3h** | **8d** (82), 50 |

[a] Decomposition.




**Scheme 4.**

**8a**, a result subsequently developed into a preparative procedure by using the parent *N*,*N*-diethyl triazenes **3e–h** (Table 2).[11b]

We tentatively suggest that a double protonation of triazenes **3**, competitive with the decomposition of mono-protonated **3** into a diazonium salt (i.e. **4**) owing to the inherently strong acidity of the medium, occurs under these conditions. In the event, fast decomposition of the formed bis-cationic species would deliver **8** alongside an ammonium triflate as observed (Scheme 4).

Whatever the validity of this hypothetical pathway, a straightforward access to aryl triflates from triazenes has been disclosed, the only unsatisfactory result being registered with the *p*-methoxy derivative **3g**, when substantial amounts of unidentified polyaromatic compounds were formed.

In summary, the use of aprotic Sandmeyer conditions has proved satisfactory for converting aristeromycin **1b** into the iodide **1e**, thence to the potentially useful carbocyclic adenosine derivative **1a**. Unexpectedly, attempted preparation of a triazene from **1b** proved difficult. Examination of a little-studied triazene-diazonium triflate conversion was more satisfactory however. A dichotomy in reactivity of aryl–dialkyl triazenes with triflic acid has been unveiled resulting in a divergent access to both aryl and arenediazonium triflates, a class of diazonium salts which, promisingly, compete with more commonly encountered stabilised diazonium derivatives both in terms of thermal stability and reactivity.

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6. Thanks are due to Aventis Pharma Dévelopement (Vitry-sur-Seine) and Rhodia (Saint-Fons) for support. Drs. M. Mulhauser (from Aventis), L. Saint-Jalmes and J.-M Paris (from Rhodia) are acknowledged for a generous gift of the amine **2** and triflic acid, respectively, and their interest. These results are taken in part from the thesis and DEA dissertation of C.P. (Strasbourg, 2003) and F.W. (Strasbourg 2001), respectively.
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11. (a) The triazenes **3a–h** were prepared as described (see references in Ref. 8). Though apparently stable (v. infra), diazonium triflates should be considered as potentially explosive and all experiments, including subsequent work-up operations were conducted behind a safety screen. *Protocol for the triazene–diazonium triflate conversion*: To a cooled (dry ice/methanol bath), well-stirred, solution of **3a** (1.12 g, 5.5 mmol) in AcOEt (46 mL) was added dropwise over 5 min freshly distilled triflic acid (1 mL; 11.3 mmol; 2 equiv). A white precipitate formed immediately. The mixture was maintained at ca. −10 °C and ether

(10 mL) was added. The solids were filtered, washed with cool ether, then dried *in vacuo*. Recrystallisation of the white solid thus obtained (acetone/ether) afforded the pure (NMR) diazonium triflate **4a** (696 mg, 47%) as colourless needles (mp 81 °C). In the case of the *p*-nitro derivative **3d**, evaporation of the solvent ($CH_2Cl_2$, owing to the poor solubility of **3d** in AcOEt) was followed by crystallisation of the resulting syrup from an acetone/ether mixture to give the triflate **4d** as a crystalline solid (82%). As previously noticed, the thermal stability of these arenediazonium triflates is remarkable. Thus brief heating of a small amount (ca. 100 mg) of the nitro derivative **4d** to 100–110 °C (oil bath) failed to induce any change on the basis of NMR analysis; (b) Elimination of the ammonium triflate at the work-up stage proved tedious with the piperidine derivatives and only *N*,*N*-diethyltriazenes **3e**–**h** were used for preparative purpose. *Protocol for the triazene-aryl triflate conversion*: **3f** (3.01 g; 16.98 mmol) was gradually added, over 2.5 h, to freshly distilled triflic acid (20 mL; 226 mmol; 13 equiv), the internal temperature being maintained at −10 °C with a cooling bath (dry ice/methanol). The resulting dark mixture was allowed to reach room temperature then stirred overnight before being poured into iced water (180 mL). The mixture was extracted with $CH_2Cl_2$ (3×45 mL), the pooled organic extracts being then washed with brine (4×60 mL), and dried ($MgSO_4$). The black oil (2.84 g) left by evaporation of the solvent was distilled (bp 90 °C at 17 $\tau$) using a short path distillation apparatus to give the triflate **8b** as a pale yellow oil (2.54 g; 66%). Selected data: **4c**: mp 55 °C; $\delta_H$ ($D_2O$): 4.09 (s, 3H), 7.37–7.44 (m, 2H), 8.45–8.53 (m, 2H); **4d**: mp 99 °C; $\delta_H$ (acetone-$d_6$): 8.84–8.91 (m, 2H), 9.2–9.28 (m, 2H); **8d**: mp 50 °C; $\delta_H$ ($CDCl_3$): 7.48 (d, $J = 9.3$ Hz, 2H), 8.35 (d, $J = 9.3$ Hz, 2H). All NMR at 200 MHz. Aryl triflates were identified by comparison with authentical samples[18] and by NMR, TLC and GLC analyses. For a review on aryl triflates, see: Ritter, K. *Synthesis* **1993**, 735–762

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