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# Synthesis of sterically encumbered and functionalized diaryl-diazenes by formal [3+3] cyclization of 2-aryldiazenyl-3-silyloxy-2-en-1-ones with 1,3-bis(silyloxy)-1,3-butadienes

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**Abstract**

Functionalized diaryl-diazenes (azo-dyes) were regioselectively prepared by formal [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 2-aryldiazenyl-3-silyloxy-2-en-1-ones.


*Keywords:* Azo-dyes; Cyclizations; Diazenes; Silyl enol ethers

Diaryl-diazenes (azo-dyes) are of outstanding importance as dyes in the field of material sciences, analytical biochemistry, analytical chemistry, and food chemistry.[1] In recent years, it has been shown that functionalized diaryl-diazenes are of increasing relevance in the field of medicinal chemistry, due to their wide range of pharmacological activity. For example, salicylic acid-derived diazene **A** (Fig. 1) has been reported to show anticancer, cytotoxic, apoptosis-inducing, antiallergic, antihistaminic, and protein-binding activity. It shows interesting transport properties in vivo and inhibits the release of leukotriene $B_4$, thromboxane $B_2$, and prostaglandin.[2] Alizarin yellow R (**B**) has been reported to act as an inhibitor of amyloid fibril formation.[3]

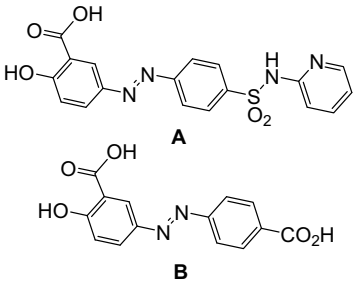


Fig. 1. Pharmacologically important diaryl-diazenes.

The classic approach to diaryl-diazenes relies on the reaction of benzene derivatives with aryldiazonium salts which involves the formation of a carbon–nitrogen bond. Although this method has been widely applied, the synthesis of more complex, heavily substituted and functionalized derivatives is difficult or not possible at all, due to steric and electronic effects. The formation of regioisomeric mixtures or undesired regioisomers is a severe problem. In addition, the synthesis of the required starting materials, substituted benzene derivatives, can be a difficult task.

An alternative strategy for the synthesis of azo-dyes relies on cyclization reactions of synthetic building blocks which already contain a diazene moiety. For example, heterocyclic azo-dyes have been prepared by the reaction of 2-aryldiazenyl-1,3-diones with guanidine,[4a] sulfuryl diamide,[4b] hydroxylamine,[4c] hydrazines,[4d,e] hydrazides,[4f] and anilines.[4g] The synthesis of diaryl-diazenes (arene-based azo-dyes) by a building block strategy has, to the

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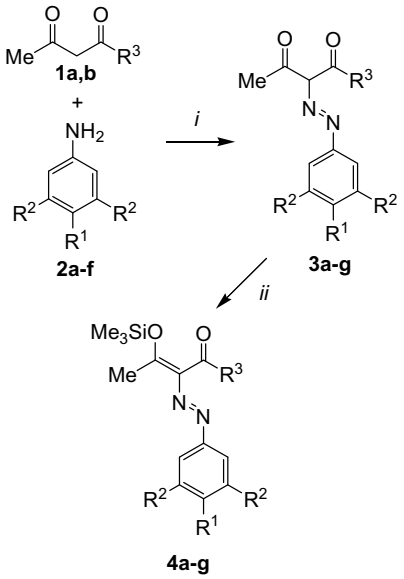
best of our knowledge, not been reported to date. Herein, we report an efficient and regioselective synthesis of diaryldiazenes by formal [3+3] cyclizations[5,6] of novel 2-aryldiazenyl-3-silyloxy-2-en-1-ones with 1,3-bis(silyloxy)-1,3-butadienes.[7] This strategy relies on the assembly of one of the arene moieties and formation of two carbon–carbon bonds. The sterically encumbered and functionalized diaryl-diazenes reported herein are not readily available by other methods.

2-Aryldiazenyl-1,3-diones **3a**–**g** were prepared by the reaction of 1,3-diketones **1a,b** with anilines **2a**–**e** (Scheme 1, Table 1).[4h] The silylation of **3a**–**g** afforded the 2-aryldiazenyl-3-silyloxy-2-en-1-ones **4a**–**g**. The $TiCl_4$-mediated reaction of **4a**–**g** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5a**–**f**, readily available from the corresponding 1,3-dicarbonyl compounds,[5] afforded the functionalized diaryldiazenes **6a**–**t** (Scheme 2, Table 2). The best yields were obtained when the reaction was carried out in a highly concentrated solution.[8] In addition, the quality of the starting materials, and the stoichiometry played an important role. The formation of **6a**–**t** can be explained by $TiCl_4$-mediated conjugate addition of the terminal carbon atom of **5** onto **4**, cyclization by attack of the central carbon atom of the 1,3-bis(trimethylsilyloxy)-1,3-butadiene onto the carbonyl group, and subsequent aromatization upon aqueous work-up. The moderate yields can be explained by an incomplete conversion (isolation of the hydrolyzed starting materials), $TiCl_4$-mediated oxidative dimerization of **5**,[9] and decomposition. In addition, the handling of each individual experiment and the chromatographic separation play an important role.

In conclusion, we reported the synthesis of diaryl-diazenes by [3+3] cyclization of 2-aryldiazenyl-3-silyloxy-2-en-1-ones with 1,3-bis(silyloxy)-1,3-butadienes. The sterically encumbered and functionalized products reported herein are not readily available by other methods.

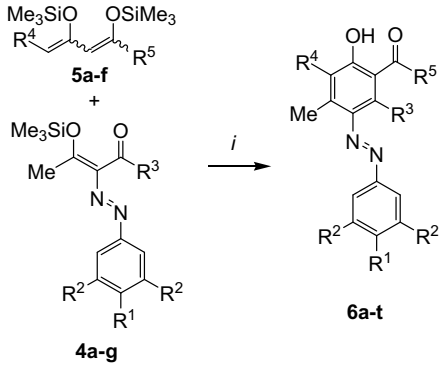



Scheme 1. Synthesis of 2-aryldiazenyl-3-silyloxy-2-en-1-ones **4a**–**g**. Reagents and conditions: (i) (1) $NaNO_2$, HCl, 0 °C, 10 min; (2) NaOAc, $H_2O$, EtOH, 0 °C, 3 h; (ii) $Me_3SiCl$, $NEt_3$, benzene, 20 °C, 48 h.

Table 1
Synthesis of **4a**–**g**

| 1 | 2 | 3, 4 | $R^1$ | $R^2$ | $R^3$ | % (3)[a] | % (4)[a] |
|---|---|---|---|---|---|---|---|
| **a** | **a** | **a** | H | H | Me | 88 | 93 |
| **a** | **b** | **b** | Cl | H | Me | 98 | 91 |
| **a** | **c** | **c** | Br | H | Me | 96 | 88 |
| **a** | **d** | **d** | *i*Bu | H | Me | 64 | 92 |
| **a** | **e** | **e** | *i*Pr | H | Me | 59 | 91 |
| **a** | **f** | **f** | H | Me | Me | 81 | 85 |
| **b** | **a** | **g** | H | H | Ph | 96 | 86 |

[a] Yields of isolated products.




Scheme 2. Synthesis of diaryl-diazenes **6a**–**t**. Reagents and conditions: (i) $TiCl_4$, $CH_2Cl_2$, −78→20 °C, 12 h.

Table 2
Synthesis of **6a**–**t**

| 4 | 5 | 6 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | %[a] |
|---|---|---|---|---|---|---|---|---|
| **a** | **a** | **a** | H | H | Me | H | OMe | 66 |
| **a** | **b** | **b** | H | H | Me | H | OEt | 60 |
| **a** | **c** | **c** | H | H | Me | Me | OMe | 30 |
| **a** | **d** | **d** | H | H | Me | Et | OMe | 51 |
| **a** | **e** | **e** | H | H | Me | OMe | OMe | 41 |
| **b** | **a** | **f** | Cl | H | Me | H | OMe | 44 |
| **b** | **c** | **g** | Cl | H | Me | Me | OMe | 35 |
| **b** | **e** | **h** | Cl | H | Me | OMe | OMe | 32 |
| **b** | **b** | **i** | Cl | H | Me | H | OEt | 40 |
| **b** | **d** | **j** | Cl | H | Me | Et | OMe | 47 |
| **c** | **a** | **k** | Br | H | Me | H | OMe | 20 |
| **d** | **a** | **l** | *i*Bu | H | Me | H | OMe | 41 |
| **d** | **c** | **m** | *i*Bu | H | Me | Me | OMe | 30 |
| **d** | **b** | **n** | *i*Bu | H | Me | H | OEt | 37 |
| **e** | **a** | **o** | *i*Pr | H | Me | H | OMe | 32 |
| **e** | **c** | **p** | *i*Pr | H | Me | Me | OMe | 31 |
| **e** | **f** | **q** | *i*Pr | H | Me | H | *t*Bu | 33 |
| **e** | **b** | **r** | *i*Pr | H | Me | H | OEt | 41 |
| **f** | **a** | **s** | H | Me | Me | H | OMe | 31 |
| **g** | **a** | **t** | H | H | Ph | H | OMe | 30 |

[a] Yields of isolated products.

## Acknowledgment

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8. *Typical experimental procedure*: To a $CH_2Cl_2$ solution (2.5 mL) of **4a** (553 mg, 1.0 mmol) and **5a** (391 mg, 1.5 mmol) was added $TiCl_4$ (209 mg, 1.1 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C within 18 h. To the mixture was added hydrochloric acid (10%) and the organic and the aqueous layer were separated. The latter was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc = 100:1→20:1) to give **6a** as a red solid (186 mg, 66%), mp = 82 °C; $R_f = 0.56$ (heptanes/EtOAc = 3:1). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.31 (s, 3H, $CH_3$), 2.61 (s, 3H, $CH_3$), 3.99 (s, 3H, $OCH_3$), 6.78 (s, 1H, Ar), 7.50 (m, 3H, N=NAr), 7.86 (d, 1H, N=NAr), 7.89 (d, 1H, N=NAr), 11.23 (s, 1H, OH). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 17.3, 20.5 ($CH_3$), 52.2 ($OCH_3$), 111.4 ($C_{Ar}$), 118.3 ($CH_{Ar}$), 122.4, 129.1, 130.9 ($CH_{Ar}$) 136.8, 137.3 ($C_{Ar}CH_3$), 145.4, 152.6 ($C_{ArN=N}$), 161.7 ($C_{Ar}OH$), 172.0 ($COOCH_3$). IR (KBr, $cm^{-1}$): 3420 (br, w), 3018 (w), 2964 (w), 2928 (w), 1672 (s). MS (EI, 70 eV): $m/z$ (%) = 284 ($M^+$, 99), 179 (100), 147 (91), 77 (59). HRMS (EI): calcd for $C_{16}H_{16}N_2O_3$ ($[M]^+$): 284.11554, found: 284.11567.
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