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New nitrogenated siloxy butadienes from 1,3-dichloroacetone

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Abstract—New 1-formamido-2-siloxy-1,3-butadienes have been generated from 1,3-dichloroacetone by means of phosphorane formation, formamido substitution, Wittig olefination and silylation. The procedure demonstrates the utility and versatility of this methodology for the formation of polysubstituted dienes, designed as useful building blocks for the synthesis of polycyclic alkaloids and related analogues.

In previous papers we described the preparation and synthetic potential of new 1-phthalimido-2-siloxy-4-aryl-1,3-butadienes[1] in the research directed to the synthesis, using the Diels–Alder cycloaddition reaction, and evaluation of new cytotoxic agents based on natural products.[2] In view of the synthetic possibilities of 2-siloxy-4-aryl-1,3-butadienes carrying a nitrogen substituent at position-1 and certain difficulties encountered during the recovery of the free amino group from the phthalimido moiety, we decided to prepare other dienes in this series.

Although there are several possibilities for introducing this type of nitrogen substituent, we chose the formamido group, because the presence of the formyl substituent not only opens the possibility of its removal, but also suggests its use for further cyclisation reactions regarding the synthesis of fused polyheterocyclic systems (Fig. 1).

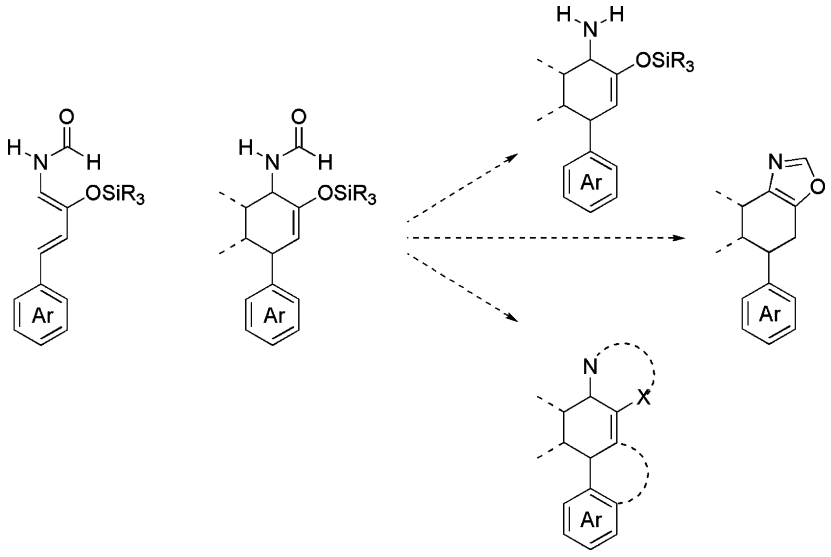

Figure 1. 1-Formamido-2-siloxy-4-aryl-1,3-butadienes and examples of their potential applications in synthesis.

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We planned our synthesis of the depicted 1-formamido-2-siloxy-4-(2-nitrophenyl)-1,3-butadienes **1**–**3** from 1,3-dichloroacetone, a useful starting material previously used in the preparation of related dienes,[3] according to the sequence in Scheme 1. As a nitrogen nucleophile we used sodium diformylamide, generated by the treatment of formamide with sodium methoxide followed by evaporation to dryness, which has been described to produce *N*-formylaminomethyl ketones and *N*,*N*-diformylaminomethyl ketones by reaction with α-haloketones.[4] The formation of these reaction products depends on the solvent used, the former being obtained in ethanol and the latter produced in acetonitrile, although both are of interest because they yield free amino groups upon treatment with HCl.[5]

In our case, the substitution reaction failed in ethanol or acetonitrile but afforded the monoformyl derivative *N*-[2-oxo-3-(triphenylphosphoranylidene)propyl]formamide (**4**) in suitable yields when dimethylformamide was used as a solvent.[6,7] The Wittig reaction of **4** with 2-nitrobenzaldehyde yielded enone **5**, which was readily converted into dienes **1**, **2** and **3** by silylenolisation with the corresponding triflates.

Once the synthesis of dienes **1**, **2** and **3** had been successfully achieved, we assayed these compounds for the Diels–Alder reaction with maleimide, a representative dienophile that is also suitable for the synthesis of polycyclic heteroaromatic compounds carrying a [*c*]-fused pyrrole ring. In the reaction of dienes **2** and **3** with maleimide, the cycloaddition products were produced under standard conditions (only ketone **5** was obtained from reactions with diene **1** because of its lower stability). After isolation and spectroscopic analysis of cycloadducts **6** and **7**, [8] the NOE effects between all the hydrogens at positions 3a,4,7,7a demonstrated that the cycloadducts produced were those derived from the *endo*-approaches between both reagents. Especially significant were the NOE effects observed on H-3a and H-7 upon irradiation of the proton geminal to the formamido group (H-4) (Fig. 2).

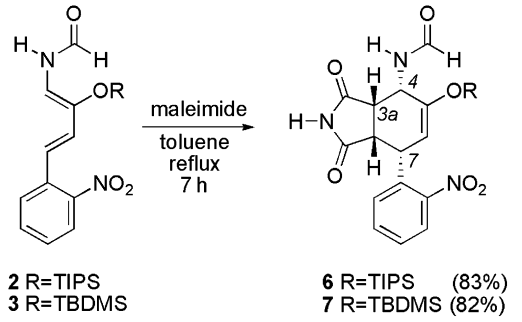
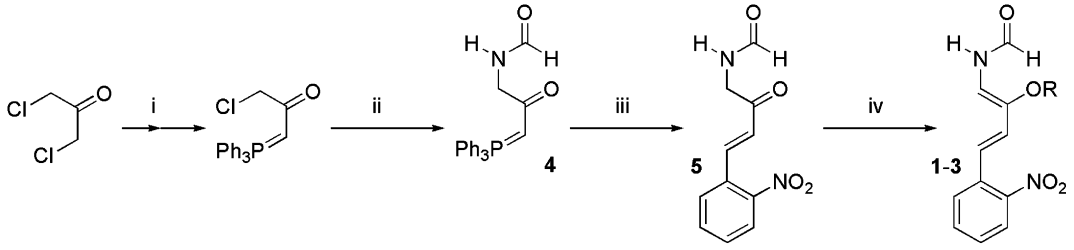


Figure 2. Diels–Alder reaction of dienes **2** and **3** with maleimide.

When we compared these products with *endo* stereochemistry with 4-phthalimido analogue **8**, which was previously identified as the *exo* isomer, we found that the spectroscopic data were very similar in all the cases. For this reason, we have now rekindled our interest in the study of the stereochemistry of this compound **8** and of the other previously published cycloadducts **9** and **10** (Fig. 3).

The *exo* stereochemistry of cycloadducts **9** and **10** was unequivocally assigned through X-ray diffraction studies.[1,9] This *exo*-cycloaddition result can be explained in terms of high crowding in the (less favourable) *endo* transition state, produced by the presence of the 1-phthalimido and 4-aryl (2-nitrophenyl, *N*-benzenesul-



Scheme 1. Synthesis of dienes **1** (R = TMS), **2** (R = TIPS) and **3** (R = TBDMS). Reagents and conditions: (i) (a) PPh_3, THF, reflux, 3 h; (b) Na_2CO_3 (0.8 mol/mol), H_2O/MeOH, rt, 30 min (65%); (ii) $NaN(CHO)_2$, DMF, 100 °C, 30 min (60%); (iii) 2-nitrobenzaldehyde, toluene, reflux, 90 min (55%); (iv) $TfOSiR_3$ (2.5–4.0 mol/mol), CH_2Cl_2, rt, 1–2 h, then Et_3N (2 mol/mol) (>90%).

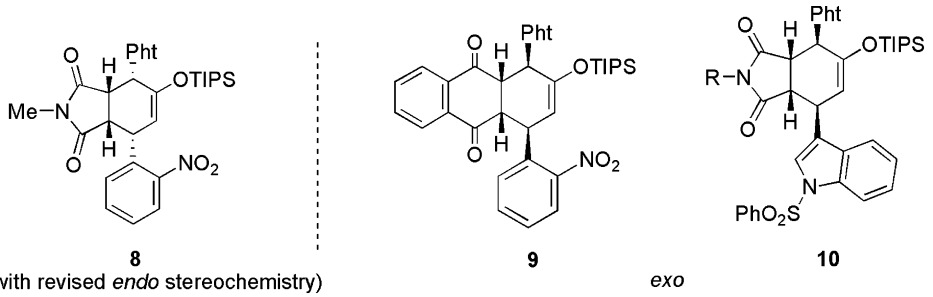


Figure 3. Cycloadducts from 1-phthalimido-2-siloxy-1,3-butadienes.

phonylindol-3-yl) substituents of the diene together with the quinone or the maleimide substituents.

Based on these results, we had also previously proposed an *exo* stereochemistry for **8**, although in this case it could not be confirmed by X-ray methods. However, comparison of NOE experiments carried out for **8** and for the new compounds **6** or **7** established that all three compounds had the same *endo* stereochemistry, such that we have now corrected the *exo* stereochemistry previously described for **8**.

In light of these results, the stereochemical course of the Diels–Alder reaction observed in previous papers[1–3] and in this work for 1-unsubstituted, 1-formamido and 1-phthalimido substituted 4-aryl-2-siloxy-1,3-butadienes is depicted in Figure 4, where the required transition states for each case are represented. The *exo* stereochemistry was produced when the 1-phthalimido and 4-aryl substituents were present, except in the case of 2-nitrophenyl at position C4 reacting with maleimide, which yielded the *endo* stereoisomer. The absence of substituents at position C1 afforded *endo* products, as was observed in the new cycloadducts described here, with the formamido group at C1. The combination of substituents around the reacting core, depending on the degree of crowding produced in each case, must be responsible for the stereochemistry of the final products.

The obtained cycloadducts can be transformed into more elaborated diverse compounds. In this respect, polysubstituted hexahydroisoindoles were obtained. Osmium tetraoxide–barium chlorate oxidation[10] of **7** produced the silylated derivative **11** [11] instead of the usually produced hydroxy-ketone.[12] The structure of this compound was established by NMR ^{1}H and ^{13}C data: the signals corresponding to the TBDMS group and to a quaternary carbon at 97.2 ppm allowed us to establish the presence of the geminal hydroxy/siloxy

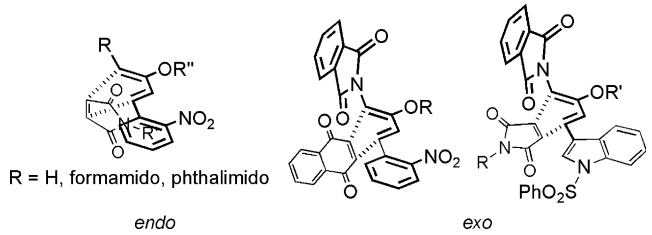


Figure 4. Transition states involved in the formation of the corresponding cycloadducts.

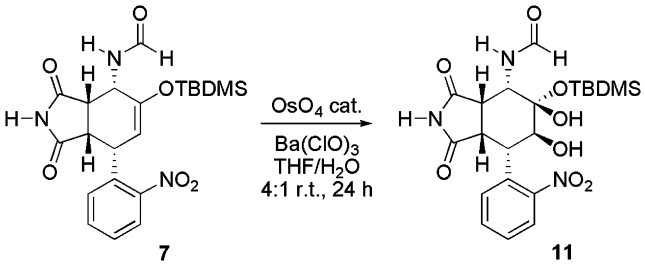


Figure 5. Reaction of cycloadduct **7** with osmium tetraoxide–barium chlorate.

moiety, whereas the secondary hydroxyl group was characterised by the signal of the hydrogen as a doublet at 4.17 ppm and the chemical shift of this carbon at 75.5 ppm. The proposed stereochemistry was deduced from the NOE effects and the couplings observed between protons H-6 and H-7 in NMR ($J = 11.0$ Hz) corresponding to a trans-diaxial disposition (Fig. 5).

In order to synthesise an oxazole-fused system, several reactions were carried out. For instance, attempts to hydrolise the siloxy group under fluoride (TBAF) or acid conditions led to unaltered **6** or **7**, whereas the use of $FeCl_3$ as a Lewis acid produced the oxazole derivative **12,** attainable from a ketoformamido intermediate, cyclisation and retro-Diels–Alder as shown in Scheme 2.

In conclusion, we describe a straightforward preparation of new 1-formamido-2-siloxy-4-aryl-1,3-butadienes of interest for the synthesis of polycyclic systems. The stereochemical outcome of their Diels –Alder reaction with maleimides is compared with that observed for related dienes; in the present case the *endo*-cycloaddition products are in agreement with the lower degree of crowding of the 1-formamido substituent upon comparison with the 1-phthalimido analogues.

Acknowledgements

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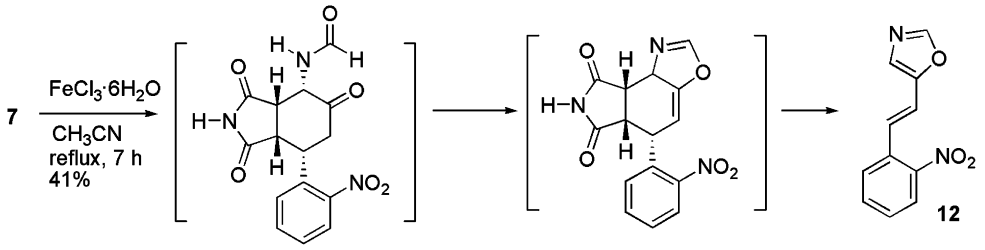

Scheme 2.

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7. In diglyme a complex mixture was produced. After a careful scrutiny of the reaction conditions, 6 mol/mol of sodium diformylamide in DMF (Ref. 5) 30 min at 100 °C produced a 60% yield of **4**. With longer periods of time or higher temperature, 3-hydroxypyrrol and triphenylphosphine oxide were obtained, from an internal Wittig reaction, as the major products.
8. Compound **7** (R = TBDMS): HRMS *m*/*z* calcd for $C_{21}H_{28}N_3O_6Si$ 446.1747, found 446.1783. ^{1}H NMR (δ ppm) 8.32 (1H, s, C*H*O); 7.96 (1H, d, $J = 8.1$ Hz, H-3′); 7.76 (1H, t, $J = 8.1$ Hz, H-5′); 7.46 (1H, t, $J = 8.1$ Hz, H-4′); 7.28 (1H, d, $J = 8.1$ Hz, H-6′); 5.01 (1H, m, H-4); 4.96 (1H, m, H-6); 4.26 (1H, m, H-7); 3.82 (1H, dt, $J = 8.3$, 1.5 Hz, H-7a); 3.48 (1H, dd, $J = 8.3$, 5.3 Hz, H-3a); 0.85 (9H, s, TBDMS); 0.15 (3H, s, TBDMS); 0.14 (3H, s, TBDMS). ^{13}C NMR (δ ppm) 178.6 (C); 175.6 (C); 161.1 (CH); 150.8 (C); 149.6 (C); 134.4 (C); 132.7 (CH); 131.8 (CH); 128.4 (CH); 124.8 (CH); 101.4 (CH); 46.1 (CH); 45.5 (CH); 45.1 (CH); 36.4 (CH); 19.0 (C); 17.7 ($3CH_3$); −4.7 (CH_3); −5.2 (CH_3).
9. Crystallographic data (excluding structure factors) for **9** and **10** are deposited at the Cambridge Crystallographic Data Centre as Supplementary data (CCDC 268250 and CCDC 200219, respectively).
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11. Compound **11**: Mp 190 °C (diethyl ether). HRMS *m*/*z* calcd for $C_{21}H_{30}N_3O_8Si$ 479.1618, found 479.1621. ^{1}H NMR (δ ppm): 8.32 (1H, s, NHC*H*O); 8.22 (1H, s, N*H*); 7.96 (1H, d, $J = 7.4$ Hz, H-3′); 7.87 (1H, d, $J = 7.0$ Hz, N*H*CHO′); 7.73 (1H, m, H-6′); 7.71 (1H, m, H-5′); 7.46 (1H, dd, $J = 7.8$, 1.2 Hz, H-4′); 4.65 (1H, dd, $J = 7.4$, 7.0 Hz, H-4); 4.17 (1H, d, $J = 11.0$ Hz, H-6); 3.82 (1H, m, H-7a); 3.80 (1H, m, H-7); 3.35 (1H, dd, $J = 9.6$, 7.4 Hz, H-3a); 0.85 (9H, s, TBDMS); 0.15 (3H, s, TBDMS); 0.14 (3H, s, TBDMS). ^{13}C NMR (δ ppm) 177.4 (C); 175.8 (C); 164.2 (CHO); 150.3 (C); 132.4 (CH); 132.1 (C); 131.7 (CH); 128.2 (CH); 124.8 (CH); 97.2 (C); 75.5 (CH); 53.3 (CH); 42.3 (CH); 40.0 (2CH); 25.8 ($3CH_3$); 17.8 (C); −2.9 (CH_3); −3.2 (CH_3).
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