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Diels–Alder reactivity and some synthetic applications of (*E*)-1-(3-indolyl)-3-*tert*-butyldimethylsiloxy-1,3-butadienes

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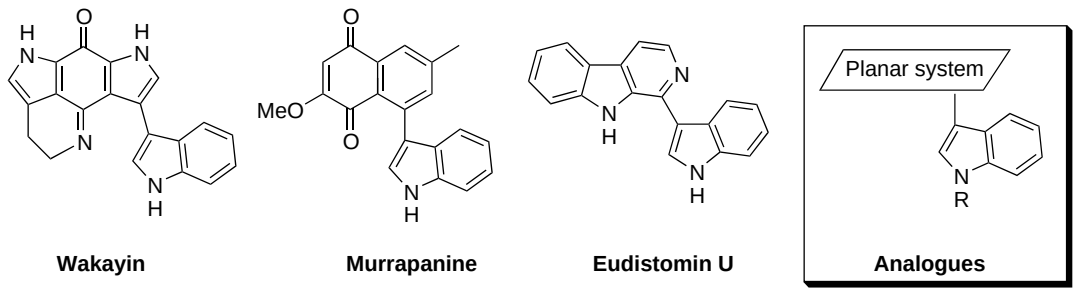
Abstract—The preparation of (*E*)-1-(3-indolyl)-3-*tert*-butyldimethylsiloxy-1,3-butadienes and their Diels–Alder reaction with selected dienophiles at room temperature is described. The utility of these heteroaryldienes for the construction of different (3-indolyl)-planar systems is shown by the synthesis of a grooved analogue of arcyriaflavin A.

Recently, we started a research project directed at the synthesis of alkaloid analogues having a (3-indolyl)-planar system as a common structural feature and taking, among others, the natural cytotoxic alkaloids wakayin,[1] murrapanine[2] and eudistomin U[3] as models.



Some of these natural models have been reported to act by inhibiting topoisomerase[4] (top) and our proposed family of analogues have the structural requirements (i.e. planar system, minor DNA groove binding unit, variable substituents on the top of the structure) described as pharmacophore for such an activity.[5] In consequence, in agreement with the postulated possible existence of a dual pharmacophore for top-1/top-2 inhibitors,[6] we expect these novel alkaloid analogues to be topoisomerase inhibitors.

The methodology selected is based on the Diels–Alder reaction of (*E*)-1-(3-indolyl)-3-*tert*-butyldimethylsiloxy-1,3-butadienes, which represents an extension (aryl to heteroaryl) of our research on the use of phenyl- and phenoxy-trialkylsiloxy-dienes for the synthesis of natural product analogues.[7] This approach has successfully been applied in our new synthesis of the indolocarbazole alkaloid arcyriaflavin A.[8]

There are few references about the Diels–Alder reactivity of 1-heteroaryl-1,3-dienes and even less about 1-heteroaryl-equivalents to Danishefsky's diene. Examples of the first group are some reported syntheses of murrapanine, yuehchukene (a dimeric alkaloid) and analogues starting from (*E*)-1-(3-indolyl)-1,3-butadienes[2,9] and a recently reported synthesis of dimeric coumarins via 7-methoxy-8-(3-methyl-1,3-butadienyl)coumarins,[10] whereas an example of the second group has been communicated by a russian group who prepared some furyl-planar systems from (*E*)-1-(2-furyl)-3-trimethylsiloxy-1,3-butadienes.[11]

Keywords: dienes; Diels–Alder reactions; indoles; alkaloids.

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In this communication we describe the preparation of (*E*)-1-(*N*-methyl-3-indolyl)-3-*tert*-butyldimethylsiloxy-1,3 - butadiene (**1**) and (*E*) - 1 - (3 - indolyl) - 3 - *tert*-butyldimethylsiloxy-1,3-butadiene (**2**), an exploratory study on their behavior in the Diels–Alder reaction and the synthesis of a grooved analogue of arcyriaflavin A, as a proof of their synthetic applications.

Dienes **1** and **2** were obtained from the corresponding indole-3-carbaldehydes (Scheme 1). The first was easily prepared by Claisen–Schmidt condensation of *N*-methylindole-3-carbaldehyde and acetone (20 equiv.) to give the corresponding enone, followed by enolsylilation with TBDMSOTf/Et_3N. As the condensation with acetone did not work well with indole-3-carbaldehyde, we used a Wittig reaction to build the appropriate enone which underwent enolsylilation to diene **2**; in this case, depending on the proportion of TBDMSOTf used, dienes **2a** or **2b** (*N*-silylated) were obtained.

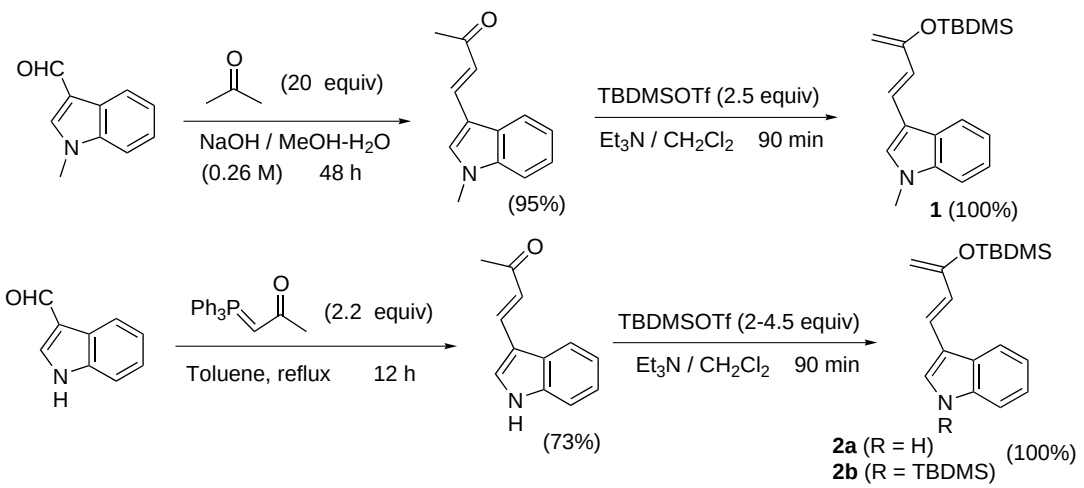
We next studied the Diels–Alder reactivity of these new dienes, against the following representative dienophiles: *N*-phenylmaleimide, *N*-methylmaleimide, 4 - phenyl - 1,2,4 - triazoline - 3,5 - dione, dimethyl acetylenedicarboxylate, 1,4-benzoquinone, 1,4-naphtoquinone and 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone.[12] The outcome of the Diels–Alder reactions[13] is summarized in Table 1; the yields were calculated by the ^1H signals integration from ^1H NMR spectra and, when possible, the reaction products were isolated either as slightly impure cycloadducts by insolubilization (diethyl ether or hexane) or as the parent ketones by hydrolysis (HCl–CH_2Cl_2 or AcOH–THF–H_2O) and crystallization. The low yields (not optimized) observed in some hydrolysis could be attributed to that this kind of compounds are prone to aromatization. It should be pointed out that the structure depicted for cycloadducts coming from reactions with dienes **2a**, **2b** or **2a**/**2b** mixtures refers to compounds with 3-indolyl and/or *N*-(*tert*-butyldimethylsilyl)-3-indolyl as the (IND) unit.

All these products were obtained as single diastereomers, originated from the expected *endo* cycloaddition, all the spectroscopic data (two-dimensional NMR, NOE experiments) and molecular modeling of transition states being in agreement with our former studies[7c,7f] on this kind of cycloadducts and their corresponding ketones generated by acidic hydrolysis of the silyl enol ether moiety.

Most of the cycloadducts or ketones in this way obtained are appropriate building blocks for the preparation of the proposed natural product analogues. As both an exploratory synthetic study and a proof of the synthetic utility of these indolyl-dienes, we have obtained[14] (Scheme 2) a grooved (between indole and pyrrolocarbazole units) analogue, **26**, of the indolocarbazole alkaloid arcyriaflavin A, following a similar approach to that used in our synthesis of this alkaloid[8] and its open analogues.[7b,7f] It is worth noting that only traces of the corresponding regioisomer of **25** from the Fischer indolization reaction were obtained.

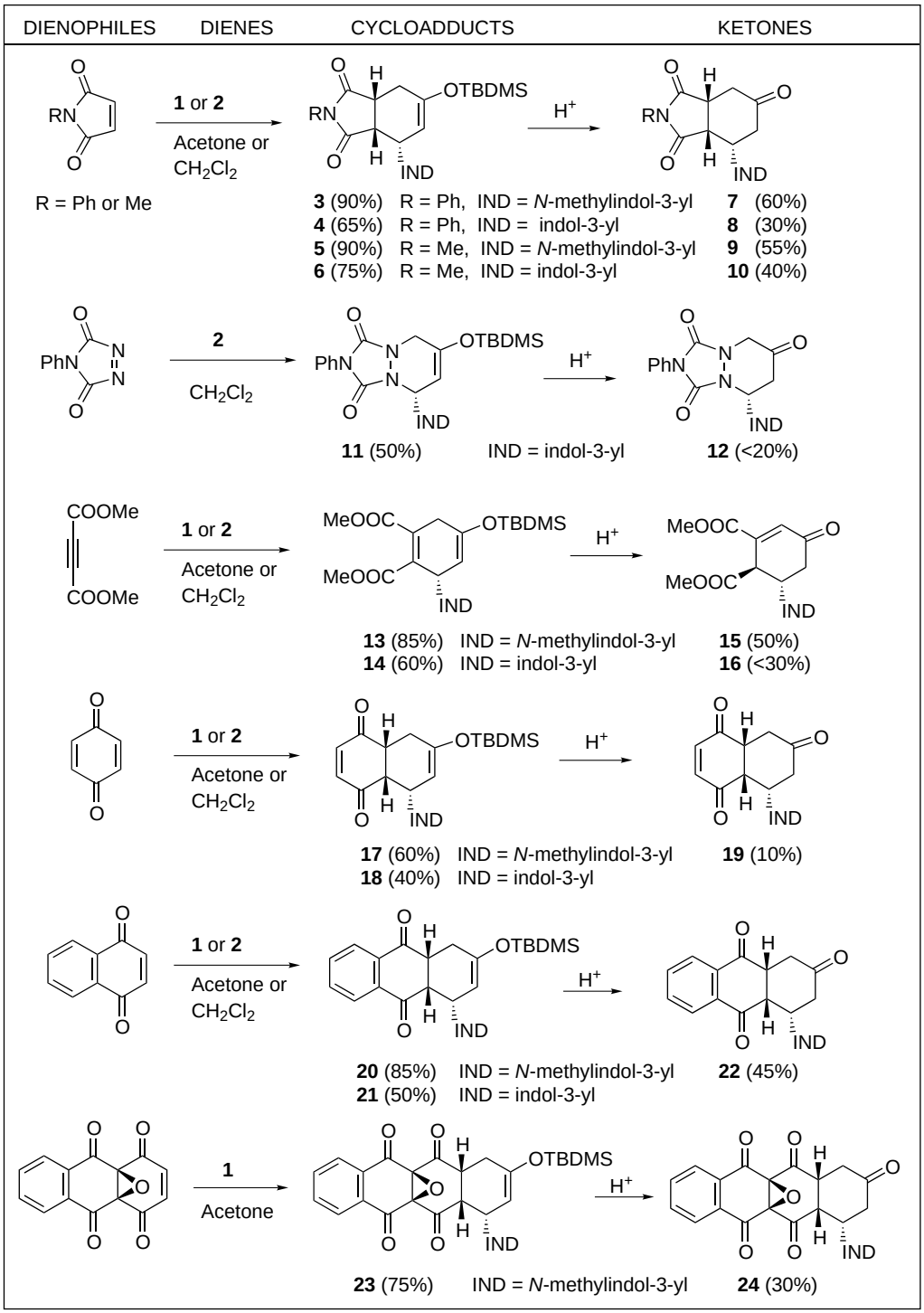
Compound **26** has the planar system (pyrrolo[3,4-*c*]carbazole) bearing the 3-indolyl unit, thus, fulfilling the general structure and being the first compound obtained within the proposed alkaloid analogues.

We are currently exploring the Diels–Alder reactivity of similar *N*-(*R*-sulphonyl)protected dienes with the aim of synthesizing with reasonable yields similar and more elaborated 3-indolyl-planar compounds with free indolic -NH-, in order to enable interactions through hydrogen bonds with the expected biological targets. The results of the cytotoxic activity of this family of natural product analogues will be communicated in due course.



Scheme 1. Synthesis of dienes **1** and **2**.

Table 1. Outcome of the Diels–Alder reactions (rt, 2 days) of **1** and **2** with selected dienophiles



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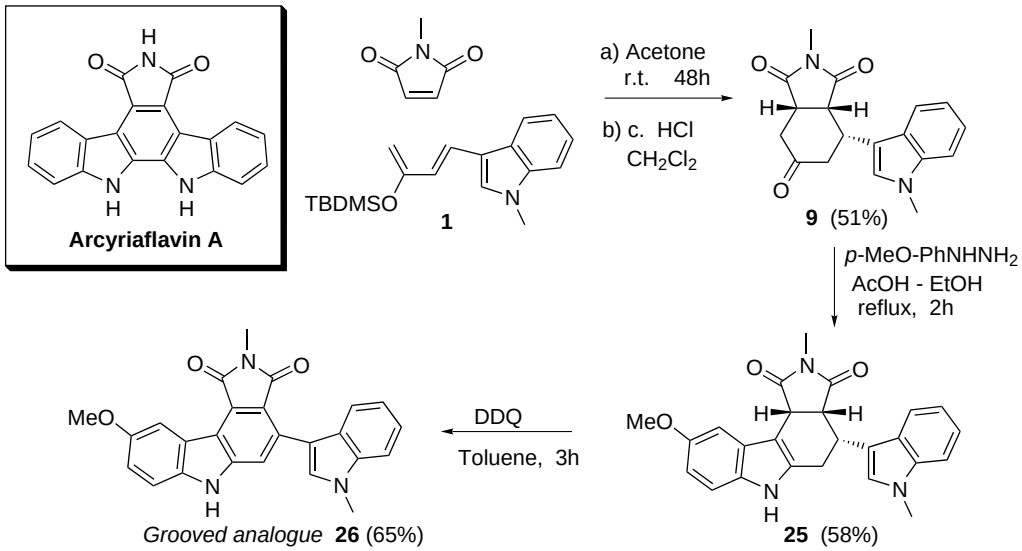

Scheme 2. Synthesis of a *grooved* analogue of arcyriaflavin A.

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13. All the reactions were carried out at room temperature, in the dark, for two days. Due to the low stability of the dienes, they were prepared and immediately reacted with the dienophiles.
14. All the analytical data for the synthesized compounds are consistent with their structure, as for instance: compound **25**, orange oil (58%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.63 (s, 3H), 3.07 (m, 2H), 3.6–3.9 (m, 2H), 3.70 (s, 3H), 3.93 (s, 3H), 4.35 (d, J=7.4 Hz, 1H), 6.86 (dd, J=8.4, 2.6, 1H), 6.99 (s, 1H), 7.20 (m, 3H), 7.22 (d, J=8.4 Hz, 1H), 7.43 (s, 1H), 7.60 (d, J=8.2 Hz, 1H), 7.95 (s, 1H). ^{13}C NMR (50 MHz, CDC_{13}): δ 24.3, 27.7, 31.4, 32.8, 41.2, 45.2, 55.9, 101.9, 104.1, 109.4, 111.5, 112.3, 113.6, 118.5, 119.1, 121.8, 127.3, 127.8, 130.8, 135.4, 136.5, 154.6, 176.7, 177.8. Compound **26**, red powder (65%). ^{1}H NMR (400 MHz, Pyr-d_5): δ 3.21 (s, 3H), 3.65 (s, 3H), 4.00 (s, 3H), 7.27 (dd, J=8.0, 8.0, 1H), 7.37 (dd, J=8.0, 8.0, 1H), 7.41 (d, J=8.0, 1H), 7.43 (dd, J=8.6, 2.6, 1H), 7.70 (d, J=8.8, 1H), 7.95 (s, 1H), 8.01 (d, J=8.0, 1H), 8.15 (s, 1H), 9.17 (d, J=2.4, 1H), HRMS: calcd for $C_{25}H_{19}N_3O_3$ [M$^+$]: 409.1426; found: 409.1655. Anal. calcd for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26; O, 11.72%; found: C, 73.30; H, 4.72; N, 10.22%.