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Diversity-oriented approach to spirooxindoles: application of a green reagent 'rongalite'

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ABSTRACT

A range of functionalized spirooxindole derivatives have been assembled via the Diels–Alder (DA) reaction. Here, rongalite has been used to generate the key sultine building blocks which are useful latent diene equivalents in the DA chemistry. The di-bromo intermediates used here are produced by reacting the 1,2,4,5-tetrakis(bromomethyl)benzene with protected oxindole derivatives under operationally simple reaction conditions. In our study, we avoided the isolation of various intermediates, and thus reduced the cost and efforts related to the overall process.

Introduction

One of the major goals of the organic as well as medicinal chemists is to synthesize simple molecules that are useful as therapeutic agents. Spirooxindole unit has been found to be core structural element in several natural and non-natural products (Fig. 1).[1] Recently, a great deal of attention has been paid for the synthesis of spirooxindoles due to their structural relevance with bioactive molecules.[2] Among the 'drug-like' small molecules, functionalized spirooxindole synthesis is rapidly growing.[3] Construction of spirooxindole framework is a challenging task because of the creation of a quaternary center which itself is considered a difficult task in synthetic organic chemistry.[4] Therefore, it is desirable to design simple strategies involving 'one-pot' synthesis[5] or without isolating the intermediates during the overall process. Ultimately, such approaches would result in reducing the cost and also the waste associated with the synthesis of these bioactive molecules.

In spite of several reports[6] for the synthesis of spirooxindole derivatives, new and general approaches with minimum number of steps from simple starting materials are highly desirable. Here, we report a new and useful strategy to deliver diverse spirooxindole derivatives by using DA reaction as a key step.[7]

Sulfones are considered to be useful synthons for the creation of C–C bonds via cationic, anionic, and radical intermediates in preparative organic chemistry.[8] Moreover, fused 3-sulfolenes are latent source of conjugated dienes, and consequently they are useful partners in DA reaction for the construction of diverse and intricate targets containing six-membered rings.[9] Interestingly, neighboring methylene moiety present in the sulfone can be alkylated with various electrophiles due the electron withdrawing nature of the sulfone group. This unique reactivity combined with the ease of desulfonylation has been exploited for assembling various interesting targets.[10] In addition, α-halogenated sulfones are valuable precursors for the Ramberg–Bäcklund reaction[11] to generate carbon–carbon double bonds. Although, several methods are reported for the synthesis of sulfone derivatives, most of them involve multi-step processes.[12] Due to this reason, simple and efficient methods to assemble sulfones are in great demand. Therefore, we are interested to synthesize the sulfone derivatives via a green reagent such as rongalite.[13] Rongalite is commonly used as a bleaching agent in printing and dyeing industry and it is also a very useful reagent in the synthetic organic chemistry.

Results and discussion

As a part of major program directed toward the development of new methodologies to spirocyclic frameworks,[14,15] we identified functionalized spirooxindole derivatives as our target. The documented difficulties in their synthesis prompted us to develop an operationally simple method from commercially available starting materials. In this context, we started our journey with the preparation of 1,2,4,5-tetrakis(bromomethyl)benzene **11** by using a known

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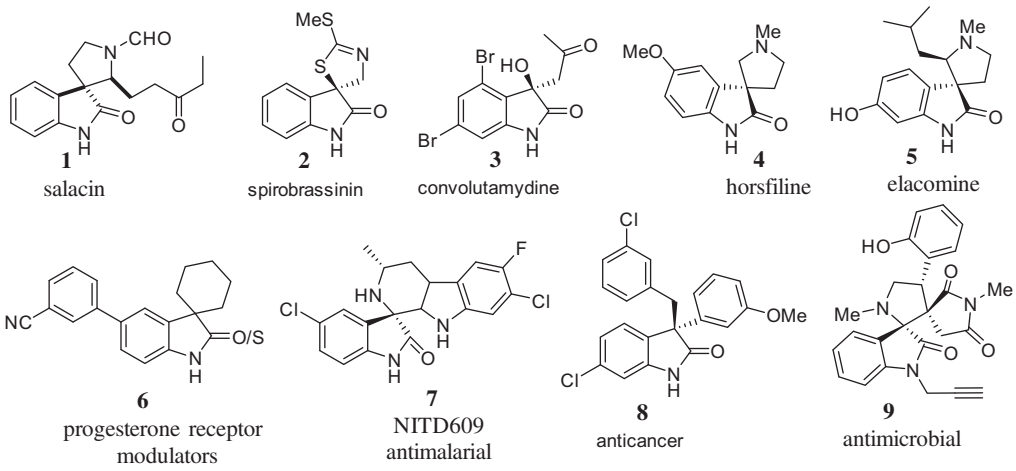


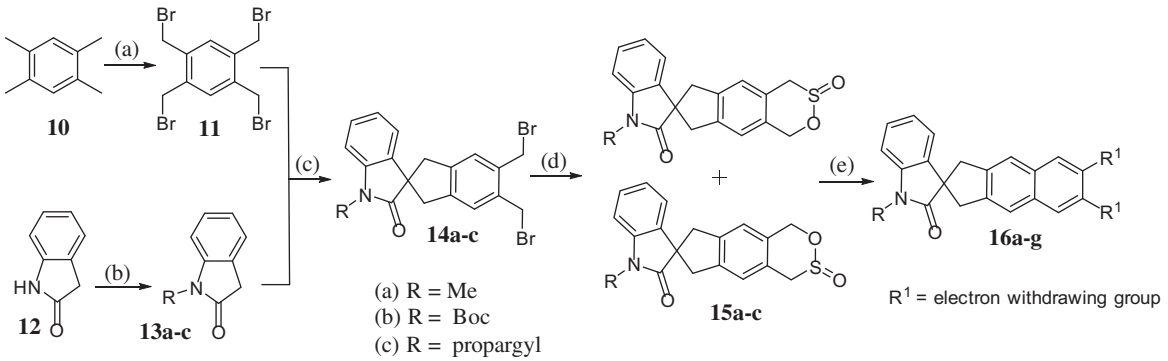
Figure 1. Structures of biologically active compounds containing spirooxindole unit.

procedure.[16] Having the tetra-bromo intermediate **11** in hand, our next task was to selectively protect the NH-group of oxindole **12**. To this end, *N*-methyl derivative was prepared from the oxindole **12** by using K_2CO_3/Me_2SO_4 in refluxing toluene to generate the desired compound **13a**, which on treatment with tetra-bromide **11** in the presence of K_2CO_3 at room temperature (rt) gave the di-bromo building block **14a** (Scheme 1). Later, the crude product **14a** was directly transformed into the sultine derivative via rongalite. The sultine derivative **15a** was then subjected to the DA reaction with tetracyanoethylene to furnish the required cycloadduct **16a** in 33% overall yield (three steps) (Table 1 and entry 1). The structure of the compound **16a** was confirmed by ^1H, ^{13}C NMR spectral data and further supported by the HRMS data.

Similarly, the DA reaction with different dienophiles such as *N*-phenylmaleimide and dimethyl acetylenedicarboxylate (DMAD) gave the corresponding cycloadducts. The DA adduct with DMAD was aromatized with MnO_2 in refluxing toluene to deliver the dehydrogenated product **16c** in 20% overall yield involving four steps (Table 1 and entry 3). To further expand the utility of this strategy, we selectively protected the oxindole **12** with the Boc-group by using $K_2CO_3/(Boc)_2O$ in MeCN to afford the expected product **13b**. Later, the Boc-protected oxindole derivative **13b** was reacted with the tetra-bromo compound **11** by using K_2CO_3 as a base in MeCN to deliver the di-bromo intermediate **14b** (Scheme 1). Next, the crude product **14b** was treated with rongalite to furnish the sultine derivative **15b**, which on treatment with tetracyanoethylene gave the desired DA adduct **16d** in good yield (Table 1 and entry 4). Surprisingly, the DA adducts with *N*-phenylmaleimide and DMAD gave the un-protected DA products due to the de-protection of the Boc-group under thermal reaction conditions (Table 1, entries 5 and 6). In addition, the scope of this methodology has been expanded by starting with the propargyl protected oxindole derivative **13c** and applying the same sequence of reactions to deliver the propargylated spirooxindole derivative **16g** in good overall yields (Table 1 and entry 7).

Later, the sultine intermediates have also been rearranged to sulfone derivatives under toluene reflux conditions (Scheme 2 and Fig. 2).

The efficiency of this methodology has been compared by synthesizing the compound **16a** following an alternative route and isolating the key intermediates during the sequence. To this end, we began with the *N*-methylated compound **13a** by converting it into the di-propargylated compound **18** (70%) with NaH/propargyl bromide in THF (Scheme 3). Later, the di-propargylated building block **18** was subjected to a [2+2+2] co-trimerization with the aid of Wilkinson's catalyst in dry EtOH in the presence of a catalytic amount of titanium isopropoxide to yield the diol intermediate **20**, which was treated with PBr_3 in CH_2Cl_2 to afford the di-bromo building block **14a** in 48% yield (two steps). Later, the di-bromo compound **14a** was converted to the sultine derivative **15a** (76%) by using rongalite in DMF, which was then reacted with tetracyanoethylene to deliver the DA adduct **16a** in 72% yield (Scheme 3).



Scheme 1. General scheme for the synthesis of spirooxindole derivatives. Reagents and conditions: (a) *N*-Bromosuccinimide, CH_2Cl_2, reflux, 500 W lamp, 24 h, 47%; (b) (i) NaH, Me_2SO_4, toluene, 2 h, 76% (compound **13a**), (ii) K_2CO_3, tetrabutylammonium hydrogen sulfate (TBAHS), $(Boc)_2O$, MeCN, 12 h, 50% (compound **13b**), (iii) K_2CO_3, TBAHS, propargyl bromide, MeCN, 15 h, 42% (compound **13c**); (c) K_2CO_3, TBAHS, MeCN, 15–24, not isolated; (d) rongalite, tetrabutylammonium bromide (TBAB), DMF, 6 h, not isolated; (e) dienophiles, toluene, reflux, 10–24 h, 20–33% overall yields (three steps).