



Tetrahedron report number 1036

Intramolecular Diels–Alder reaction as a key step in tandem or sequential processes: a versatile tool for the synthesis of fused and bridged bicyclic or polycyclic compounds

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ARTICLE INFO

Article history:

Received 23 September 2013

Received in revised form 15 February 2014

Accepted 18 February 2014

Available online 3 March 2014

Keywords:

Diels–Alder

Natural product

One-pot

Sequential

Tandem

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Abbreviations: IMDA, intramolecular Diels–Alder; IMHDA, intramolecular hetero Diels–Alder; DA, Diels–Alder; IEDDA, intramolecular inverse-electron-demand Diels–Alder; DAIB or DIB, diacetoxyiodobenzene; PIFA, phenyliodine bis(trifluoroacetate); PIDA, phenyliodine(III) diacetate; BTIB, bis(trifluoroacetoxy)iodobenzene; IBX, 2-iodoxy-benzoic acid; DMP, Dess–Martin periodinane; PDC, pyridinium dichromate; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; *p*-TsOH, *para*-toluene sulfonic acid; TFA, trifluoroacetic acid; CSA, camphorsulfonic acid; MSA, methanesulfonic acid; TEA, triethylamine; DIPEA, *N,N*-diisopropylethylamine; DMAP, 4-(*N,N*-dimethylamino)pyridine; TBS or TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; PMB, *para*-methoxybenzyl; BOM, benzyloxymethyl; TASF, tris(dimethylamino)sulfonium difluorotrimethylsilicate; DIBA, diisobutyl adipate; EDDA, ethylenediamine diacetate; MOB, masked *ortho*-benzoquinone; BHT, butylated hydroxy toluene; MW, microwave; DCC, 1,3-dicyclohexylcarbodiimide; THF, tetrahydrofuran; DMSO, dimethyl sulfoxide; DCE, 1,2-dichloroethane; DCB, 1,2-dichlorobenzene; TIPB, 1,3,5-triisopropylbenzene; NMR, nuclear magnetic resonance; NOE, nuclear Overhauser enhancement; DFT, density functional theory.

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1. Introduction

Two or more reactions when carried out in a single pot experiment, they are usually termed as tandem reactions.^{1,2} When these reactions take place in sequential manner they may be termed as sequential or cascade or domino reaction where each further reaction depends upon the success of preceding reaction. Such processes often involve reactive intermediates, which are usually difficult to isolate and hence are prepared in situ and used immediately.

Development of tandem or sequential processes is a rapidly growing area of synthetic organic chemistry and is a powerful methodology for efficiently synthesizing complex multinuclear molecules. Tandem or sequential reactions display high atom economy and are often accompanied by impressive selectivity. Tandem reactions involve multiple bond formation in one-pot and thus lead to reduction in the amount of byproducts, solvents, eluents, time and energy as it does not involve workup and isolation of many intermediates, thereby contributing to the protection of the environment. The combination of powerful synthetic methods in one-pot reaction sequences provides a variable access to a wide range of products with high complexity. The tandem or sequential processes involving IMDA reaction as the key reaction for the synthesis of fused and bridged bicyclic or polycyclic compounds has been extensively used over the past decade, which finds broad application in the synthesis of natural products.

The IMDA reaction^{3–5} was first reported by Kurt Alder in 1952, which led to a significant number of elegant synthetic achievements. There are two types of connectivity available to the intramolecular variant of the Diels–Alder reaction:

- (a) Type 1 in which diene and dienophile are joined at position 1 of the diene, the cycloaddition results in the formation of fused bicyclic adduct (Fig. 1).

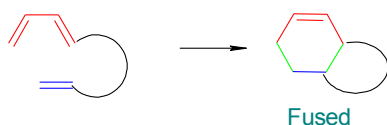


Fig. 1. Type 1 IMDA.

- (b) Type 2 in which diene and dienophile are joined at position 2 of the diene, results in the formation of a bridged bicyclic compound. The product of the Type 2 IMDA reaction contains bridgehead double bond, which is an anti-Bredt alkene and thus is very important as only few methods yield such compounds (Fig. 2).

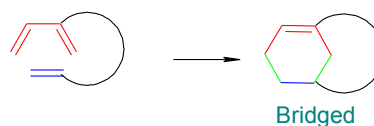


Fig. 2. Type 2 IMDA.

Diels–Alder reaction, which would be doomed to fail in the intermolecular version can be sometimes carried out using intramolecular version. Since, in IMDA cycloaddition, the two reacting functionalities are part of the same molecule, it results in less negative activation entropies and thus increases the reaction rates. IMDA reaction often results in pronounced regio- and stereo-selectivity. The regioselectivity of the reaction may be controlled by the appropriate choice of substituents in both the diene and dienophile. The topology (*endo* or *exo*) may be influenced by the electronic and functional nature of the groups attached to the dienophile and also renders the reaction diastereoselective. Side reactions such as dimerization or polymerization can be avoided by using high dilution or low pressure in gas phase. The IMDA cycloaddition can be considered for the synthesis of any molecule containing six-membered ring fused to a second ring.

In the recent years, intramolecular Diels–Alder cycloaddition in combination with other organic reactions through tandem or sequential manner is pursued for the construction of several important bicyclic or polycyclic compounds. In this review, we have covered such combinations employed during the last decade. We have broadly classified the tandem or sequential processes involving IMDA as the key reaction into following categories.

2. In situ generation of diene

2.1. Oxidative dearomatization followed by IMDA

Oxidative dearomatization of a phenol and a subsequent IMDA cycloaddition is an efficient method for the construction of structurally complex polycyclic compounds. Exposure of phenolic substrates to oxidizing agents such as $\text{Pb}(\text{OAc})_4$, DAIB, PIFA, NaIO_4 , etc. generates dienones, which are highly reactive species and thus difficult to handle as they are prone to undergo dimerization. The generation and IMDA trapping of such dienones have provided an elegant approach to a variety of structurally diverse organic compounds.

2-Methoxy-4,6-dimethyl-phenol was oxidized with DAIB in the presence of *trans*-crotyl alcohol to generate masked *o*-benzoquinone **1** in situ, which underwent IMDA cycloaddition to yield the tricyclic β,γ -enone **2** in 87% yield. The tricyclic compound **2** was

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