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New indium-mediated cyclisation reactions of tethered haloenynes in aqueous solvent systems

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Dedicated with great respect to Professor Steven V. Ley on the occasion of his 60th birthday

Abstract—The intramolecular cyclisation of tethered allyl bromides onto terminal alkynes mediated by metallic indium proceeds smoothly and cleanly in mixtures of THF and H_2O to give unsaturated carbocycles and heterocycles in good yield. Alternatively, the cyclisation may be carried out in anhydrous THF with the aid of acid catalysis. The reaction is also mediated by a range of indium salts and proceeds with substoichiometric quantities of indium in the presence of a co-reductant. Deuteration studies show that the reaction proceeds via a concerted *syn* carboindination of the carbon–carbon triple bond to give an intermediate, which is protonated in situ.

1. Introduction

In recent years there has been a great deal of interest in the application of indium to organic synthesis.[1] Indium-mediated Barbier[2] and Reformatsky-type[3] reactivity of organoindium reagents derived from allylic and propargylic precursors with a wide range of C=O and C=NR derived functional groups[4] are well-documented, and the synthetic utility of these methods has been demonstrated in the synthesis of a number of pharmaceutical and natural products.[5] The addition reactions of allylic indium reagents to carbonyl-derived electrophiles proceed with high diasteroselectivity via predominantly γ-addition of the organometallic, although the ratio of α:γ-addition has been found to be dependent on solvent.[6] Additionally, indium-mediated methodology has also been extended to take in a wide range of transformations including Michael additions,[7] indium hydride[8] and dissolving metal reductions,[9] and Pd(0) catalysed cross-coupling reactions of organoindium reagents.[10] Additionally, indium reagents have been used to facilitate radical cyclisation[11] and atom transfer cyclisation reactions.[12]

In view of the obvious importance of indium-mediated reactions, it is therefore surprising that the reactions of organoindium reagents with carbon–carbon and carbo-heteroatom triple bonds have received comparatively little attention. In early work, Araki et al. reported the addition reactions of allylic indium sesquihalides with alkynols[13] and allenols[14] to give (*E*)-2,5-hexadien-1-ols and (*E*)-2,6-heptadien-1-ols, respectively. They showed that the addition of the organoindium reagent occurs regioselectively in the anti-Markovnikov mode, which it was proposed arose as a result of coordination of the intermediate organometallic species by the hydroxyl group, which directs addition to the terminal carbon of the alkyne. Subsequently the carboindination of unactivated terminal alkynes,[15] which do not bear an adjacent hydroxyl group, to give 1,4-dienes via Markovnikov addition and the carboindination of nitriles to give enamines[16] was reported. Thus, while the synthetic scope and mechanistic aspects of the intermolecular carboindination of alkynes and nitriles have received attention, the corresponding intramolecular carboindination of alkynes with allyl halides remains is much less well understood.

In the intramolecular reaction manifold, a number of potential reaction pathways may be considered. For example, it may be reasoned that exposure of tethered haloenynes **1** (X=O, NR, CR^1R^2) to indium metal would give the corresponding allylindium species **2a** which could exist in equilibrium with the *endo* isomer **2b**. Furthermore,

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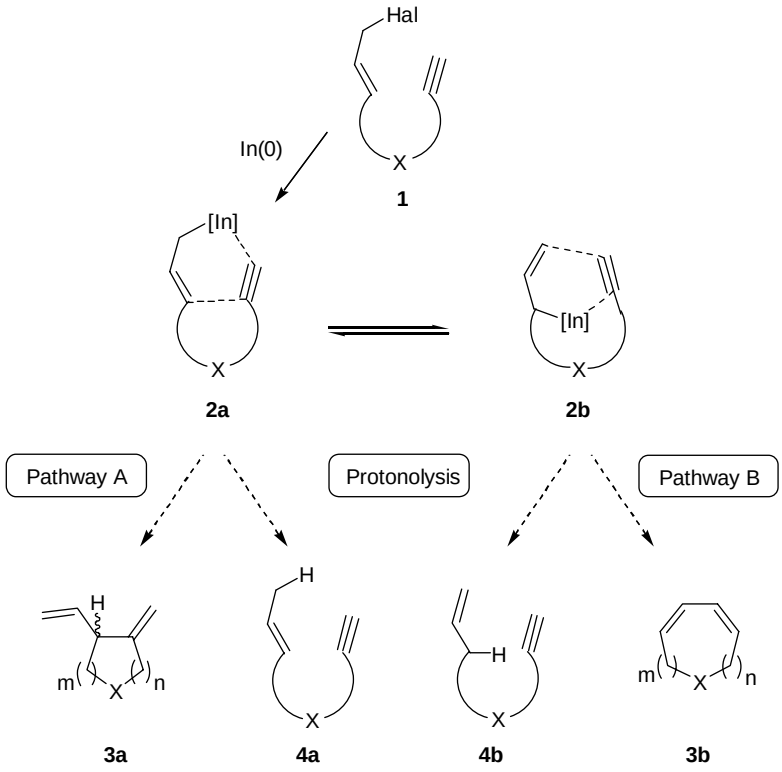
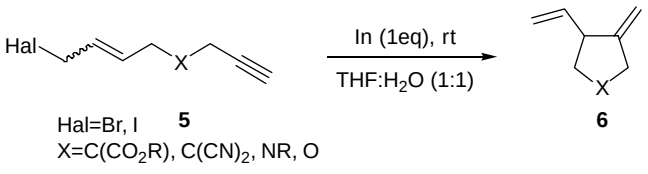


Scheme 1. Possible pathways for the reaction between indium and haloallylalkynes.

such intermediates could be expected to react by (i) a process of carboindation of the alkyne triple bond by either a Markovnikov (pathway A) or *anti*-Markovnikov (pathway B) route to give the corresponding *exo* 1,4-dienes **3a** or *endo* 1,3-dienes **3b**, respectively[17] or (ii) proteodebromination of the organometallic (for example, on workup) to give either the crotyl **4a** or allylic species **4b**. At the outset of our work, it was not clear whether the cyclisation reaction was possible or whether the pathway of proteodebromination would predominate (Scheme 1).

We herein report[18] that a broad range of bromooct-6-en-1-ynes **5** undergo smooth cyclisation at room temperature in the presence of indium metal via pathway A to give *exo*-1,4 carbocyclic and heterocyclic dienes **6** cleanly (Scheme 2). Whilst the cyclisation of enynes to five-membered carbocycles and heterocycles under the influence of a range of transition metals has been previously demonstrated[19] these procedures often necessitate the use of expensive catalysts and/or ligands, which are often moisture and air sensitive or must be prepared in situ immediately prior to use. In contrast, not only is the method discussed in the current submission robust, operationally simple and relatively inexpensive, in fact the efficiency of the reaction



Scheme 2. Indium-mediated cyclisation of tethered terminal haloallylalkynes.

is greatly enhanced by the addition of water to the reaction solvent.

2. Results and discussion

2.1. Initial approaches to the indium-mediated cyclisation reaction

The first substrate chosen for investigation was the parent bromoenyne, (*E*)-1-bromobut-2-ene-4-ol propargyl ether **7a**, which may be readily synthesized from propargyl alcohol and *trans*-1,4-dibromobut-2-ene. In a typical procedure **7a** and indium powder (1 equiv) were suspended in the appropriate solvent and stirred at room temperature or reflux for 12–21 h, before being subjected to standard aqueous acidic workup (Table 1).

Initial results using these conditions were not encouraging. Neither stirring an equimolar mixture of **7a** and indium powder in dry THF (entry 1) or dry DMF (entry 2) under an N_2 atmosphere at room temperature led to the formation of the desired cyclised product but only to recovery of unchanged starting material. Heating the reaction to reflux in dry THF in line with the protocol reported for the corresponding intermolecular reaction[15] also failed to yield any of the cyclised product **8a** (entry 3). However, to our delight when the reaction was carried out in a 1:1 mixture of THF/H_2O overnight, followed by mild protolytic workup, the desired 3-vinyl-4-methylenetetrahydrofuran **8a** was obtained in 62% yield (entry 4) as a single product. This result represents the first example of an intramolecular carboindination of alkynes, and is testament to the profound effect that the addition of water is known to have on