Organic LETTERS

Letter

pubs.acs.org/OrgLett

Conversion of Ester Moieties to 4-Bromophenyl Groups via Electrocyclic Reaction of Dibromocyclopropanes

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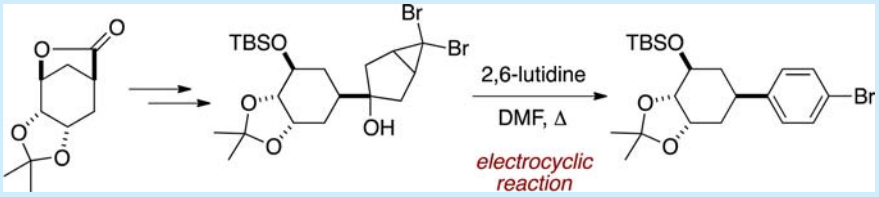
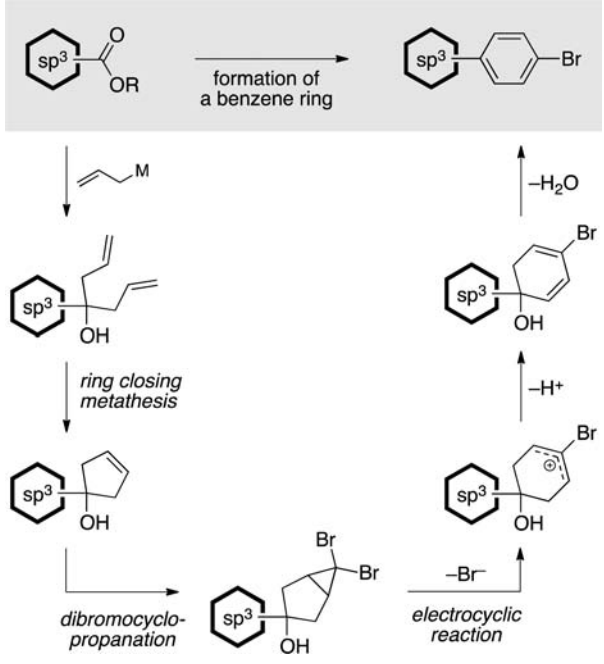
Supporting Information



ABSTRACT: Conversion of ester moieties into 4-bromophenyl groups was effected by means of a four-step protocol: a Grignard reaction of the ester with allylmagnesium halides, a ring-closing metathesis, dibromocyclopropanation, and an electrocyclic reaction of the dibromocyclopropanes.

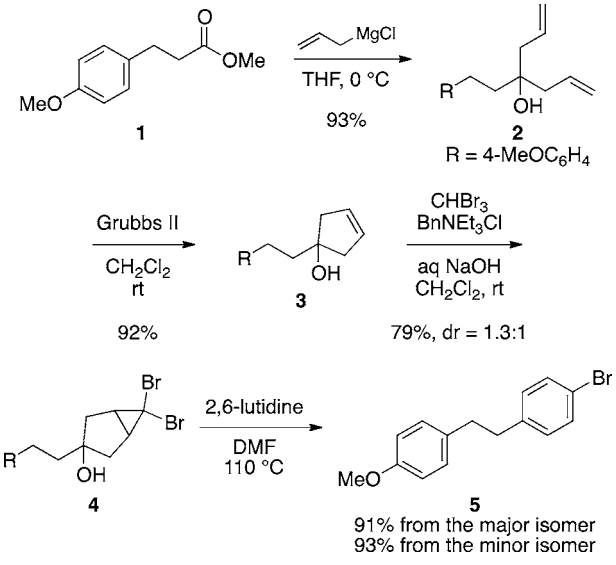
Ester and its related functional groups are ubiquitous in natural products and medicinally important compounds.

Scheme 1. Working Hypothesis



Ester moieties are also widely used in organic synthesis to construct skeletons and to introduce functional groups. Such transformations are achieved by means of a wide variety of reactions, including an aldol reaction, conjugate addition to an unsaturated ester, Diels–Alder reaction, and Ireland–Claisen rearrangement, to name a few. These reactions can transform substrates into products with more complex structures, in which chiral centers are newly created. It occurred to us that conversion of the ester moiety in such products into a benzene ring would provide versatile molecules for drug development. This is because additional complexity of the molecules might correlate positively with success in drug development.[1] In addition, benzene rings have been widely used to fine tune molecules in the course of lead optimizations by changing

Scheme 2. Formation of a Benzene Ring



Received: May 7, 2015
Published: June 12, 2015

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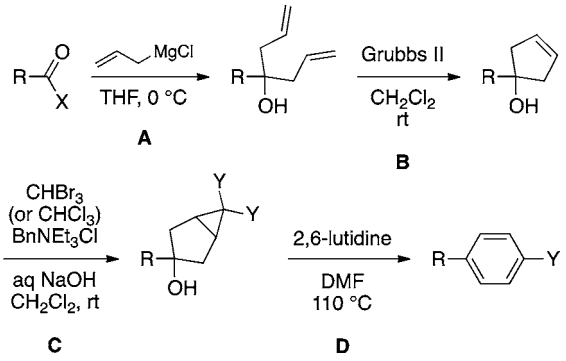
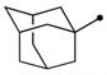
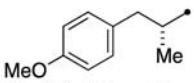
DOI: 10.1021/acs.orglett.5b01351
Org. Lett. 2015, 17, 3191–3193

Table 1. Substrate Scope



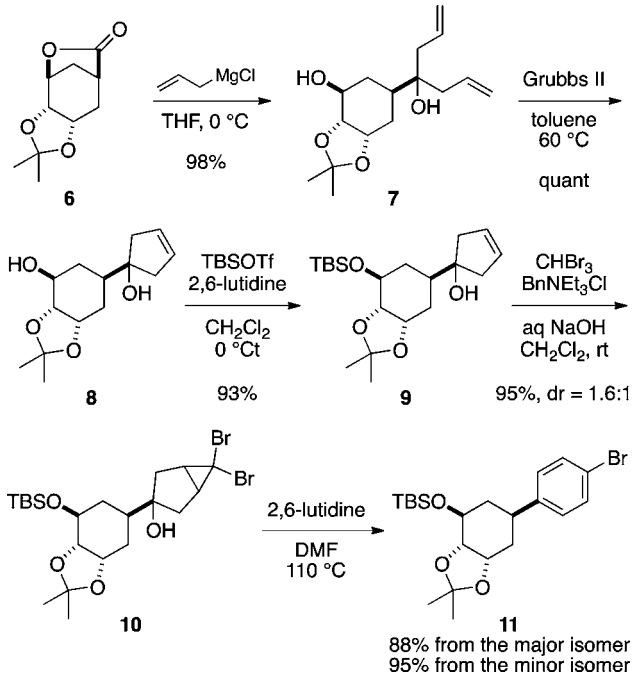
entry	R—, X, Y	yield (%)[a] A	B	C	D
1	 X = OMe, Y = Br	90	91	91[b]	90[c] 86[d]
2	 X = OMe, Y = Br	96	76	75[e]	94[c] 96[d]
3	 X = OMe, Y = Br	97	90	85[f]	90[c] 90[d]
4	 X = OMe, Y = Br	70	88[g]	82[h]	90[c] 87[d]
5	 X = OMe, Y = Br	70	85[g]	84[i]	83[c] 84[d]
6	 X = OMe, Y = Cl	-	-	88[j]	83[k,c] 81[k,d]
7	 X = (*R*)-4-benzyl-2-oxooxazolidin-3-yl Y = Br	76[l,m]	96	71[n]	93[c,o] 97[d,o]

[a]Isolated yield. [b]dr = 3:1. [c]From the major isomer. [d]From the minor isomer. [e]dr = 1.7:1. [f]dr = 2.7:1. [g]The reaction was performed in toluene at 60 °C in the presence of the second-generation Grubbs catalyst. [h]dr = 4:1. [i]dr = 2.5:1. [j]dr = 4.5:1. [k]The reaction was performed at 130 °C. [l]Allylmagnesium bromide and diethyl ether were used as a reagent and a solvent, respectively. [m]er = >99:1. [n]dr = 2:1. [o]er = >99:1.

substituents on it.[2] Along this line, we initiated our studies toward conversion of ester moieties into benzene rings.[3]

Our working hypothesis is shown in Scheme 1. A reaction of an ester with an allyl metal species would afford a tertiary alcohol that could be converted into a cyclopentenol via a ring-closing metathesis. Subjection of the cyclopentenol to cyclopropanation with dibromocarbene would furnish a dibromocyclopropane. An electrocyclic reaction of the dibromocyclopropane followed by deprotonation of the resulting allyl cation[4] would give a diene, which, after dehydration, is expected to yield a 4-bromobenzene.[5]

Scheme 3. Application to a Lactone



Our hypothesis was initially validated using ester **1** as the starting material (Scheme 2). Thus, allylmagnesium chloride was added to afford alcohol **2**, which was subjected to a ring-closing metathesis using the second-generation Grubbs catalyst[6] in dichloromethane at room temperature to afford cyclopentenol **3** in 92% yield.[7] Treatment of **3** with bromoform under basic conditions in a biphasic system furnished dibromocyclopropane **4** as a 1.3:1 mixture of diastereomers. To our delight, upon heating **4** in DMF at 110 °C in the presence of 2,6-lutidine, the electrocyclic reactions of both diastereomers occurred, giving the desired product **5** in good yield.

Having established a novel method for forming benzene rings, we next applied the method to a variety of substrates. Table 1 summarizes the results. The substrates with steric hindrance around the ester moiety could be converted to the corresponding products in good yield (entries 1 and 2). Methyl benzoate could be used as a substrate to give 4-bromobiphenyl (entry 3). Boc and Cbz groups were used to protect the amino groups and were compatible with these reaction conditions (entries 4 and 5). Chloroform could be used for the cyclopropanation, giving a dichlorocyclopropane as an intermediate, which could be converted into a chlorobenzene derivative (entry 6). *N*-Acyloxazolidin-2-one could be used as a substrate in place of the esters for this method (entry 7).[8] The stereogenic center at the α-position to the carbonyl group was conserved during the process, and no racemization was observed. *N*-Acyloxazolidin-2-ones have been used as substrates in a variety of enantio- and diastereoselective reactions.[9] These results ensured the applicability of our method to the synthesis of complex molecules.

The method thus developed was applied to lactone **6** (Scheme 3).[10] The Grignard reaction of **6** with allylmagnesium chloride and the subsequent ring-closing metathesis proceeded

DOI: 10.1021/acs.orglett.5b01351
Org. Lett. 2015, 17, 3191−3193

smoothly. After protection of the secondary hydroxy group in **8** with a TBS group, the cyclopropanation and ensuing electrocyclic reactions were conducted under the standard conditions to give **11** in good yield.

In conclusion, we have demonstrated an efficient method for constructing benzene rings from ester moieties. A variety of functional groups survived the process, and the stereogenic center at the α position to the carbonyl group was not affected by the transformation. 4-Bromo- and 4-chlorophenyl groups thus prepared are good substrates for a variety of coupling reactions.[11,12] Therefore, the method developed here will help prepare a wide range of compounds for drug development. Further applications of our method are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01351.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by JSPS KAKENHI (Grant Nos. 25221301 and 26713001) and Platform for Drug Discovery, Informatics, and Structural Life Science (MEXT). H.U. is a Research Fellow of JSPS.

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(10) Lactone **6** was synthesized from commercially available cyclohex-3-enecarboxylic acid in four steps, involving iodolactonization, elimination of hydrogen iodide, stereoselective dihydroxylation, and protection as an acetonide. For details, see the Supporting Information.

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DOI: 10.1021/acs.orglett.5b01351
Org. Lett. 2015, 17, 3191−3193