

Intramolecular Conjugate Addition of Alkenyl and Aryl Functions to Enones Initiated by Lithium–Iodine Exchange

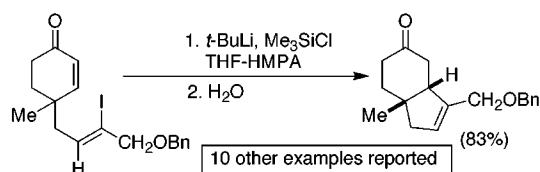
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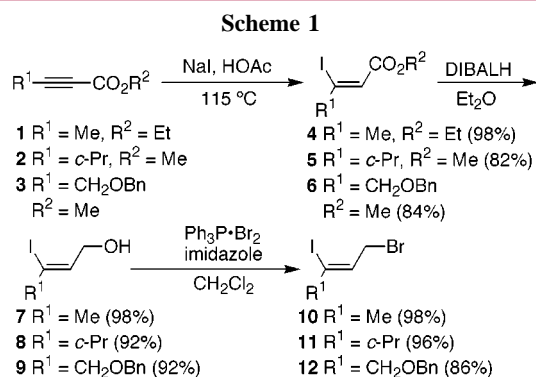
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ABSTRACT



Treatment of each of the substrates 20–26, 29, and 46–48 with *t*-BuLi in THF, in the presence of HMPA and TMSCl, provides good-to-excellent yields of the intramolecular conjugate addition products 30–36, 37, and 49–51, respectively.

A previous report¹ from this laboratory described a new procedure for the efficient, diastereoselective preparation of alkyl (*Z*)-3-iodoalk-2-enoates from alkyl alk-2-ynoates. For example (Scheme 1), treatment (115 °C, 1.5 h) of ethyl but-



2-ynoate (**1**) with a suspension of NaI (1.6 equiv) in a small amount of HOAc (6.4 equiv) provided enoate **4** in 98% yield.

(1) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816.

This experimentally simple protocol is general, and esters **5**² and **6**, which are also employed in the current study, are easily prepared from alkynoates **2**³ and **3**,⁴ respectively. Reduction of esters **4–6** with DIBALH, followed by reaction of the resultant alcohols **7–9** with Ph₃P⁺Br₂ in the presence of imidazole,⁵ provides the iodo bromides **10–12**, respectively. We reasoned that substances such as **10–12** could serve as effective synthetic equivalents of synthons of general structure **13**, which, when combined with synthons **14** as shown schematically in eq 1, would produce bicycles **15**. It turns out that this idea can readily be put into practice and, accordingly, annulation products of general structure **15** can be produced efficiently. The final step of the overall process involves a newly developed method for effecting intramolecular conjugate addition of alkenyl functions to α,β -unsaturated ketones.

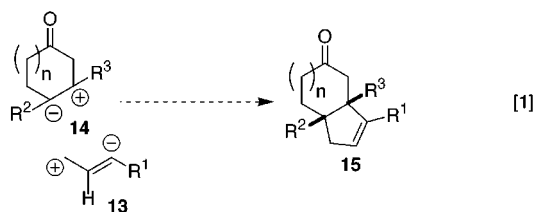
The substrates employed in this study were prepared via

(2) All new compounds reported herein exhibited spectra (IR and ¹H and ¹³C NMR) in accord with assigned structures and gave satisfactory elemental (C, H) combustion analyses and molecular mass determinations (high-resolution mass spectrometry).

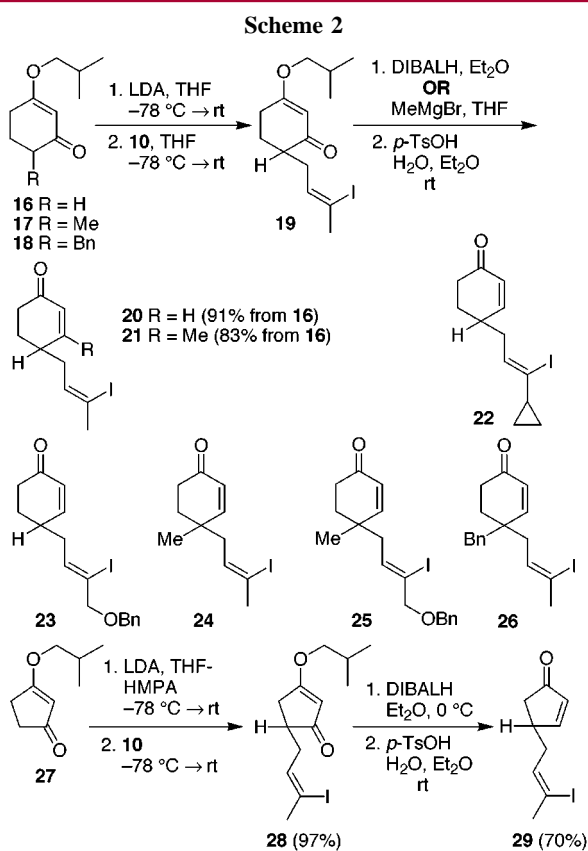
(3) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron* **1989**, *45*, 363.

(4) Sauer, D. R.; Schneller, S. W.; Gabrielsen, B. *Carbohydr. Res.* **1993**, *241*, 71.

(5) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Org. Chem.* **1964**, *86*, 964.



an efficacious method,⁶ employing the β -alkoxy enones **16**, **17**, and **18** as starting materials. For example, alkylation of **16** with bromide **10** afforded **19**, which, upon sequential subjection to reduction and acid hydrolysis, gave enone **20** (Scheme 2). On the other hand, reaction of **19** with MeMgBr,



followed by acid hydrolysis of the product, provided **21**. In a similar fashion, each of the enones **22–26** was prepared by use of the appropriate vinylogous ester (**16**, **17**, or **18**) and the required alkylating agent (**10**, **11**, or **12**). Finally, the cyclopentenone substrate **29** was analogously derived from the enone **27**⁷ and the allylic bromide **10** (Scheme 2).

Preliminary experiments toward effecting intramolecular conjugate additions initiated by lithium–iodine exchange⁸ involved conversion of substrate **20** into the known bicyclic

Table 1. Intramolecular Conjugate Additions of Alkenyl Functions Initiated by Lithium–Iodine Exchange

1. *t*-BuLi (~2.2 equiv), HMPA (~2.5 equiv), TMSCl (~4 equiv), $-78\text{ }^{\circ}\text{C}$, 5 min, then warm to rt over ~15 min
 2. H_2O

entry	starting material	product (yield, %)
1	20 R ¹ = Me, R ² = R ³ = H	30 (91)
2	21 R ¹ = R ³ = Me, R ² = H	31 (72)
3	22 R ¹ = <i>o</i> -Pr, R ² = R ³ = H	32 (96)
4	23 R ¹ = CH ₂ OBn, R ² = R ³ = H	33 (78)
5	24 R ¹ = R ² = Me, R ³ = H	34 (85)
6	25 R ¹ = CH ₂ OBn, R ² = Me, R ³ = H	35 (83)
7	26 R ¹ = Me, R ² = Bn, R ³ = H	36 (81)

29

37 (78)

ketone **30**⁹ (see Table 1, entry 1). A number of experimental parameters were investigated, including (a) the nature of the alkyllithium reagent used to effect lithium–iodine exchange, (b) the use of the additives HMPA and TMSCl, and (c) the reaction time and temperature. It was found that, although either BuLi or *t*-BuLi could be profitably employed, the latter reagent generally gave superior results (cleaner reactions, better yields) and, consequently, was used throughout the remainder of this study. It was also found that both HMPA and TMSCl had (independent) salutary effects on the yields of **30** and, when used together, further enhanced reaction efficiency. Finally, the most efficient transformations were realized when a *t*-BuLi solution was added to a cold ($-78\text{ }^{\circ}\text{C}$), stirred solution of substrate **20**, dry HMPA, and freshly distilled TMSCl in THF. Thus, these exploratory investigations led to the development of an experimental procedure¹⁰ that consistently produced good-to-excellent yields of the conjugate addition products. The results derived from use of substrates **20–26** and **29** are summarized in Table 1.

A perusal of the data given in Table 1 shows that, not unexpectedly, the placement of an alkyl group on the β -carbon on the enone acceptor function has a (minor) deleterious effect on reaction efficiency (cf. entries 1 and 2). On the other hand, the cyclization process appears to

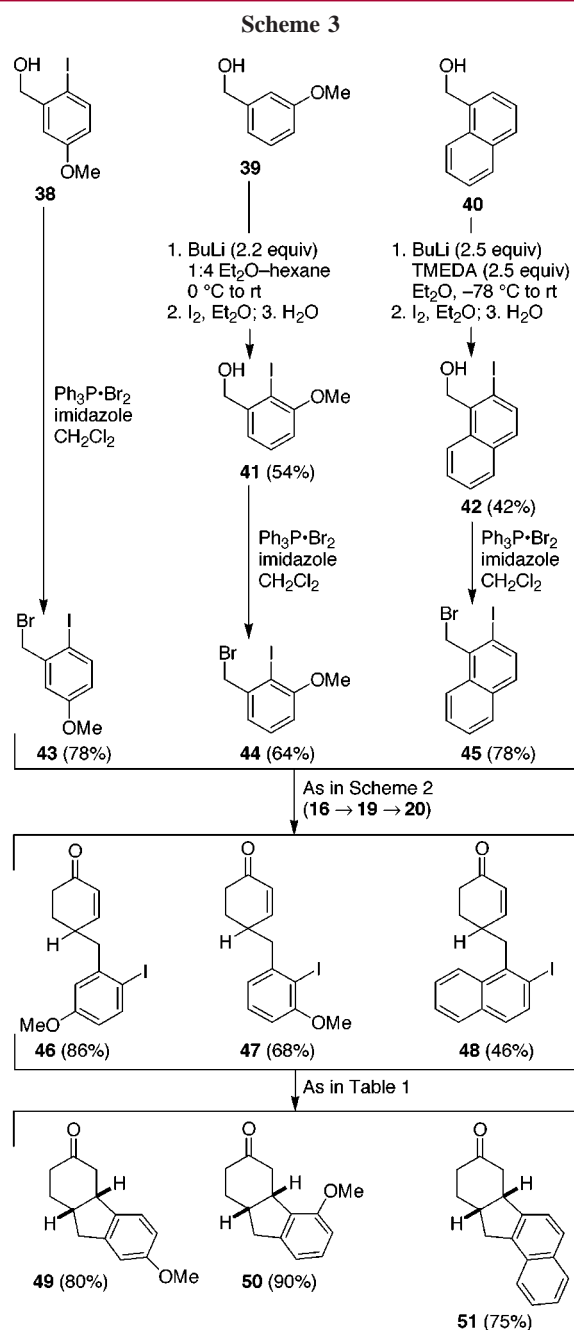
(10) The following procedure, involving conversion of **20** into **30**, is typical. A solution of **20** (99 mg, 0.36 mmol), dry HMPA (146 μL , 0.84 mmol), and freshly distilled TMSCl (203 μL , 1.6 mmol) in dry THF (5 mL), under an atmosphere of argon, was stirred at room temperature for 5 min and then was cooled to $-78\text{ }^{\circ}\text{C}$. The cold solution was treated with *t*-BuLi (1.4 M solution in pentane, 600 μL , 0.84 mmol) and, after the mixture had been stirred for 5 min, it was warmed to room temperature over a period of 15 min. The mixture was treated with 1 mL of water and then was stirred for 1 h. The phases were separated, and the aqueous phase was extracted with Et₂O (3 \times 5 mL). The combined organic extracts were washed (brine), dried (MgSO₄), and concentrated under reduced pressure. Flash chromatography (6 g of silica gel, 4:1 petroleum ether–Et₂O) of the crude oil afforded 49 mg (91%) of pure **30** as a colorless oil.

(6) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775. Stork, G.; Danheiser, R. L.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414.

(7) Panouse, J.; Sanič, C. *Bull. Soc. Chim. Fr.* **1956**, 1272.

(8) For related studies, see: Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381.

(9) Piers, E.; McEachern, E. J.; Burns, P. A. *Tetrahedron* **2000**, *56*, 2753.



tolerate structurally diverse groups on the alkenyl carbon that is involved in the lithium–iodine exchange process (entries

1, 3, 4, and 6). The examples in which R¹ = CH₂OBn (entries 4 and 6) are particularly satisfying, since the ether function provides a “handle” for subsequent synthetic manipulations. Finally, the efficient synthesis of the rather strained bicyclo-[3.3.0]oct-6-en-3-one **37** is also noteworthy (entry 8).

The successful methodological work outlined above led us to study the possibility of effecting similar intramolecular conjugate additions of *aryl* functions to enones. The syntheses of the chosen substrates **46–48** and subsequent conjugate addition results are summarized in Scheme 3. Directed *ortho*-metalation¹¹ of 3-methoxybenzyl alcohol (**39**) and 1-naphthylmethanol (**40**), followed by reaction of the acquired aryllithium intermediates with iodine, afforded alcohols **41** and **42**, respectively. Treatment of each of the alcohols **38**,¹² **41**, and **42** with Ph₃P·Br₂–imidazole in dichloromethane provided the corresponding benzylic bromides **43–45**, which, when employed as alkylating agents in reaction sequences very similar to those summarized in Scheme 2 (see **16** → **19** → **20**), furnished the enones **46–48**, respectively.

When compound **46** was subjected to reaction conditions essentially identical with those developed for the ring closure of substrates **20–26** and **29** (Table 1), the tricycle **49** was produced in 80% yield (Scheme 3). Similarly, the intramolecular conjugate addition reactions involving substrates **47** and **48** were readily performed and efficiently provided the structurally novel substances **50** and **51**, respectively.

In summary, a new protocol for effecting intramolecular conjugate additions of alkenyl and aryl functions to enone acceptors has been developed. The chemistry involved is relatively simple, and it is clear that the method could readily be employed for the construction of structurally diverse bi-, tri-, and tetracyclic compounds.

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Supporting Information Available: Procedures for the preparation of and characterization data for all new organic intermediates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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