Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest Paper

Formal carbo [3+3] annulation and its application in organic synthesis

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ARTICLE INFO

Article history:
Received 30 October 2014
Revised 16 December 2014
Accepted 2 January 2015
Available online xxxx

Keywords:
Cyclization
Cycloaddition
Annulation
[3+3]
Carbocycles

ABSTRACT

This review describes a set of approaches to generate functionalized carbocycles via [3+3] annulation and their usefulness for synthesizing frameworks of natural products. This approach relies heavily on the 1,3-dianion/1,3-dielectrophile strategy for annulations of ketones, enamines, 1,3-bis(silyl enol ethers), and other 1,3-dianionic synthons.

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Introduction

Six-membered carbocycles, which include cyclohexane, benzene, and their derivatives, occur as structural cores in a variety of biologically and pharmaceutically active products. Examples of such products include (+)-pancratistatin,[1] (−)-tetrodotoxin,[2] and other nitrogen-containing polyhydroxylated cyclohexane derivatives, which display a range of biological antitumor, anti-ulcer, and anti-infective properties. The benzene derivative hydrangenol shows cytotoxic activity against human gastric cancer cell lines,[3] while the benzene derivatives thunberginols C, D, and E promote adipogenesis in murine 3T3-L1 cells.[4]

The importance of six-membered carbocycles in synthetic chemistry makes them attractive synthetic targets. Particularly noteworthy synthetic strategies involve Diels–Alder reaction ([4+2] fashion),[5] Robinson annulation reaction,[6] double Michael cyclization ([4+2],[7a,b] and [5+1][7c]), and [2+2+2] cycloaddition.[8] Although [3+3] annulation is widely used to construct heteroatom-containing six-membered rings,[9a–d] the carbo [3+3][9e] reaction has rarely been reported in the literature. In 1979, Chan et al., applied the [3+3] reaction to arene synthesis,[10a] and much

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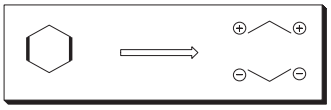
http://dx.doi.org/10.1016/j.tetlet.2015.01.035
0040-4039/

later Langer achieved $TiCl_4$-catalyzed annulation of 1,3-bis(silyl enol ethers) with 1,3-dielectrophiles using a variety of substrates and reaction conditions.[10b] Cyclohexane derivatives can be obtained via α,α′-annulation of enamines with *bis*electrophiles such as ethyl α-(bromomethyl)acrylate[11] and the substrate scope and efficiency of this reaction has been promoted rapidly along with the prosperity of organocatalysis.[12]

These classic approaches to the carbo [3+3] reaction are increasingly inadequate for meeting the needs of modern chemistry. As a result, a wide array of organocatalytic, metal-catalyzed, and even co-catalyzed asymmetric [3+3] annulations have been developed. These methodologies can be classified according to the electronic properties of the two, three-carbon synthons that participate in the reaction (Fig. 1). Type **I** carbo [3+3] annulations involve the one-step or stepwise coupling of 1,3-dianions with 1,3-dielectrophiles. Type **II** reactions involve the addition of anions to electrophiles, followed by free radical cyclization.

Type I: 1,3-Dianion/1,3-dielectrophile strategy



α,α′-Annulation of ketones

In 1959, Jung reported his discovery of [3+3] annulation of cyclohexanone **1** with enone **2** in KOH/EtOH (Scheme 1).[13] Subsequently esterification with diazomethane generated the more complex bicyclo[3,3,1] **3**. The mechanism was postulated to involve tandem Michael/aldol addition of the α and α′ carbons of **1** to enone **2**.

In 1997, Katritzky discovered that benzotriazole acts as an efficient neutral leaving group. This helped them generate heteroaromatized pyridine derivatives from 2-(benzotriazol-1-yl)acetamide and 2-(benzotriazol-1-yl)acetonitrile.[14] It also allowed them to

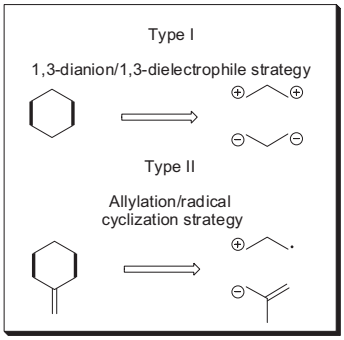
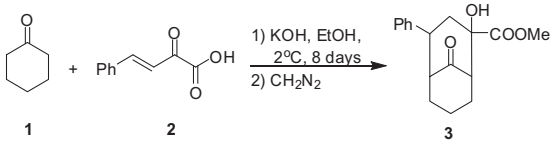
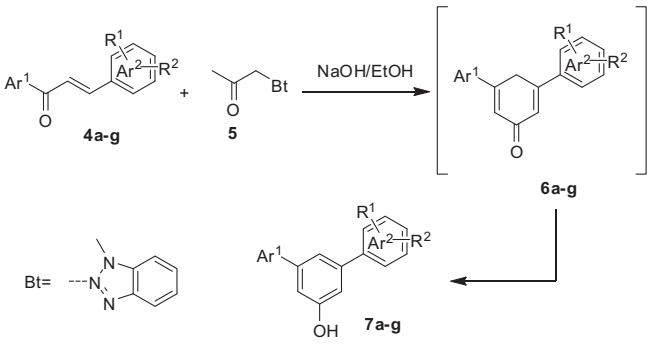


Figure 1. Type I and II carbo [3+3] annulations.



Scheme 1. Jung's [3+3] annulation.



a: Ar^1 = Ph, R^1 = R^2 = H 75%

b: Ar^1 = 4-MeO-Ph, R^1 = 4-Me, R^2 = H 72%

c: Ar^1 = Ph, R^1 = 4-Cl, R^2 = H 91%

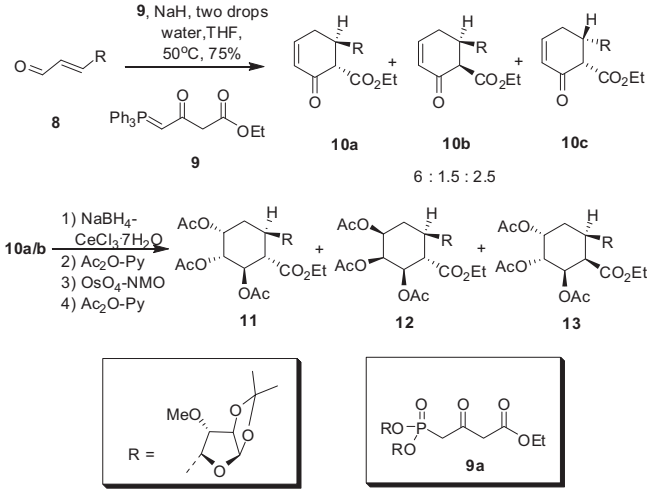
d: Ar^1 = Ph, R^1 = 4-NO_2, R^2 = H 76%

e: Ar^1 = 4-Cl-Ph, R^1 = 4-Cl, R^2 = H 94%

f: Ar^1 = 1-naphthyl, R^1 = 3-NO_2, R^2 = H 82%

g: Ar^1 = Ph, R^1 = 2-Cl, R^2 = 4-Cl 52%

Scheme 2. Katritzky's [3+3] annulations.



Scheme 3. Sharma's [3+3] annulation.

synthesize 3,5-diaryl-substituted phenols (Scheme 2).[15] In this procedure, 1-(benzotriazol-1-yl)propan-2-one **5** was first prepared from bromoacetone with benzaltriazol, and then it was subjected to tandem Michael addition/intramolecular aldol condensation with 1,3-diarylprop-2-enones **4a**–**g** under basic conditions. Subsequent leaving of benzotriazole gave the intermediates **6a**–**g**. After rearrangement, the 3,5-diaryl-substituted phenols **7a**–**g** were obtained in moderate to good yields. Electron-deficient Ar^1 or Ar^2 facilitated this reaction (**7c**–**7f**), while 2-substituted Ar^2 hindered it (**7g**).

In 2000, Sharma et al. reported their progress toward synthesizing the C–C linked pseudo-saccharide precursors **11**–**13** (Scheme 3).[16a,17] These reactions serve their larger goal of transforming sugars into *C*-glycosides, C-C linked disaccharides, and C-linked spiro saccharides. In their [3+3] approach, those authors used the more delocalized ylide **9** instead of the more nucleophilic phosphonate **9a**, ensuring that Michael addition would precede Wittig olefination.[16b] During 3-oxo-4-(triphenyl-phosphorylidene)-but-