Tetrahedron 69 (2013) 3747–3773

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Tetrahedron report number 1003

Tandem Michael–Dieckmann/Claisen reaction of *ortho*-toluates—the Staunton–Weinreb annulation

Christopher D. Donner [a,b]

[a] *School of Chemistry, The University of Melbourne, Victoria 3010, Australia*
[b] *Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Victoria 3010, Australia*

ARTICLE INFO

Article history:
Received 19 February 2013
Available online 14 March 2013

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1. Introduction

The development of methodology for the synthesis of polycyclic aromatic compounds has attracted much interest over a long period of time, often in response to the significant biological activity displayed by both natural and synthetic compounds fitting this broad structure class. Amongst a variety of common strategies used to prepare such compounds, cycloaddition and annulation methodologies, such as Diels–Alder cycloadditions,[1] [2+2+2] cyclotrimerizations,[2] benzannulation of chromium carbene complexes

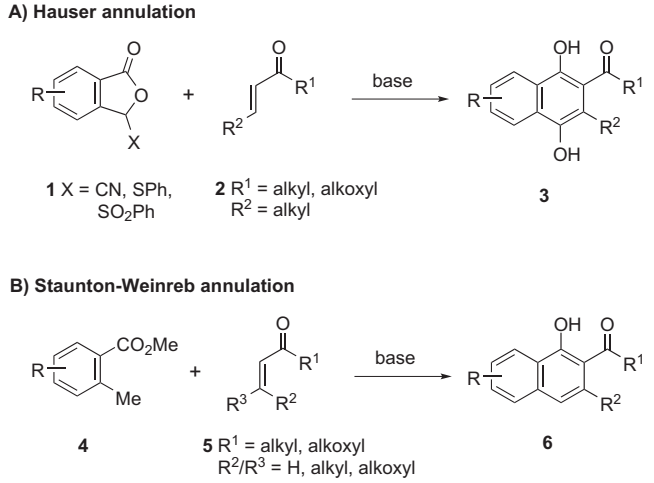
Abbreviations: Ac, acetyl; acac, acetylacetonate; 9-BBN, 9-borabicyclo[3.3.1]nonane; Bn, benzyl; Boc, *tert*-butyloxycarbonyl; BOM, benzyloxymethyl; brsm, based on recovered starting material; Bz, benzoyl; CAN, ammonium cerium(IV) nitrate; Cbz, benzyloxycarbonyl; CD, circular dichroism; CSA, camphorsulfonic acid; DCC, *N,N′*-dicyclohexylcarbodiimide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; DHP, 3,4-dihydro-2*H*-pyran; DIBAL-H, diisobutylaluminium hydride; DMAP, 4-dimethylaminopyridine; DME, 1,2-dimethoxyethane; DMP, Dess–Martin periodinane; DMPU, *N,N′*-dimethylpropyleneurea; DMS, dimethyl sulfide; DMSO, dimethylsulfoxide; DMT, bis-(4-methoxyphenyl)phenylmethyl; EOM, ethoxymethyl; HMPA, hexamethylphosphoric triamide; LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisilazide; MCPBA, *meta*-chloroperoxybenzoic acid; MEM, methoxyethoxymethyl; MOM, methoxymethyl; Ms, methanesulfonyl; NBS, *N*-bromosuccinimide; NMO, 4-methylmorpholine *N*-oxide; PCC, pyridinium chlorochromate; PIFA, bis(trifluoroacetoxy)iodobenzene; Piv, pivaloyl; PMB, 4-methoxybenzyl; PPTS, pyridinium *para*-toluenesulfonate; rt, room temperature; *p*-TsOH, *para*-toluenesulfonic acid; TBAF, tetra-*n*-butylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; TES, triethylsilyl; Tf, triflate; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran; THP, tetrahydropyran; TIPS, triisopropylsilyl; TMEDA, *N,N,N′,N′*-tetramethylethylenediamine; TMS, trimethylsilyl; TosMIC, toluenesulfonylmethyl isocyanide; TPP, tetraphenylporphyrin; Trisyl, 2,4,6-triisopropylbenzenesulfonyl; Ts, *para*-toluenesulfonyl.

E-mail address: cdonner@unimelb.edu.au.

0040-4020/$ – see front matter
http://dx.doi.org/10.1016/j.tet.2013.03.034

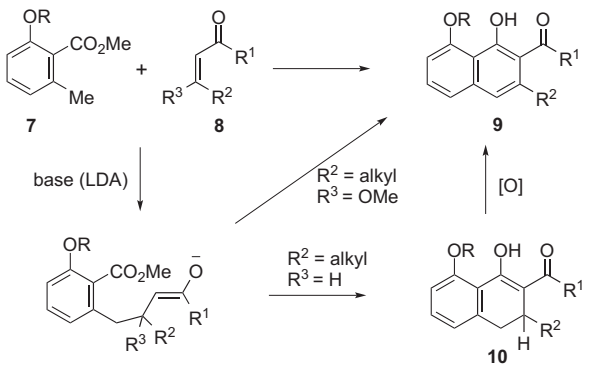
(Dötz benzannulation),[3] Danheiser benzannulations[4] and a variety of other benzannulation approaches,[5] as well as metathesis-based methods,[6] have been of broad synthetic utility.

Two further, closely related annulation procedures used to construct polycyclic aromatic systems are the Staunton–Weinreb and Hauser annulations (Scheme 1). The Hauser annulation (Scheme 1, A) the more commonly applied of these approaches,[7] utilizes stabilized phthalide anions, derived from substrates, such as **1** upon treatment with base, which undergo a tandem Michael addition–Dieckmann cyclization reaction with the Michael acceptor **2**. Following in situ aromatization, the outcome of this process is the production of polycyclic aromatic systems (**3**) with *para*-dihydroxylation in the newly formed ring, a strategic outcome particularly in the synthesis of what are often polyketide-derived natural products isolated at the quinone-level of oxidation.



Scheme 1. Annulation strategies based on a tandem Michael addition–Dieckmann or Claisen condensation reaction.

A variation of the Hauser annulation is the Staunton–Weinreb annulation (Scheme 1, B) in which an *ortho*-toluate is used as the nucleophile, replacing the stabilized phthalide used in the former process. The use of an *ortho*-toluate has subtle, but significant, implications in the overall tandem Michael–Dieckmann/Claisen reaction. With the toluate **4** being at a lower oxidation level to a phthalide, reaction with Michael-acceptor **5** results in formation of polycyclic aromatics at a correspondingly lower oxidation state (i.e., naphthol **6**, as opposed to hydroquinone **3**). As outlined in Scheme 2, when the electrophile contains a leaving group at the β-position (e.g., **8**, R^3=OMe) aromatization using **7** leads directly to naphthol products, such as **9**. However, when a leaving group is not present on the electrophile then tetralones, such as **10** can be isolated and, if desired, further oxidized to give naphthol products.

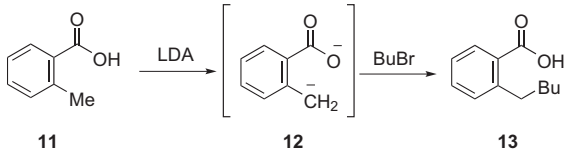


Scheme 2. Staunton–Weinreb annulation approach to naphthols **9** and tetralones **10**.

Since the first reports over 30 years ago by both Staunton[8] and Weinreb[9] on the use of *ortho*-toluate anions in tandem Michael–Dieckmann/Claisen processes, the use of this procedure has seen application in the synthesis of a variety of polycyclic systems. This review serves to highlight the scope and application of the tandem Michael–Dieckmann/Claisen reaction of *ortho*-toluates with α,β-unsaturated carbonyl electrophiles, commonly referred to as the Staunton–Weinreb annulation, in the synthesis of polycyclic structural frameworks including naphthopyranones, pyranonaphthoquinones, dihydroanthracenones, tetralones and tetracyclines.

2. Background—formation and reactivity of *ortho*-toluate anions

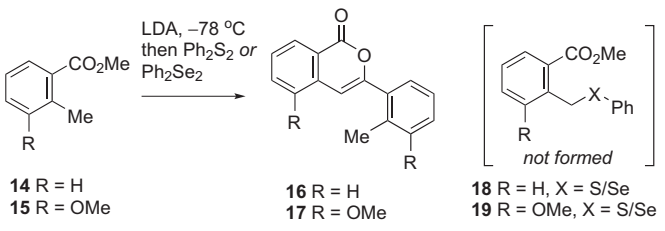
The formation of dianions of toluic acids and their subsequent alkylation was first reported by Creger.[10] Using *ortho*-toluic acid **11**, lateral lithiation[11] with LDA allows formation of the dianion **12** with subsequent addition of alkyl halide leading to the isolation of *C*-alkylated product **13** (Scheme 3). The reasonable stability of dianions, such as **12** and related substituted systems has allowed them to be applied in synthesis.[12]



Scheme 3. Alkylation of *ortho*-toluic acid **11**.

Unlike the dianions formed from *ortho*-toluic acid **11**, the anions formed from *ortho*-toluates **14** and **15** were shown to undergo exclusively dimerization to give **16** and **17**, respectively, in preference to sulfenylation or selenation to form **18** or **19** (Scheme 4).[13] Dimer **16** was also formed when trapping was attempted with ethyl crotonate as a Michael acceptor.[14] However, with an oxygen substituent *ortho* to the ester group, such as is seen in **20** (Scheme 5), the carbanion **21** can be readily formed, exhibiting a characteristic deep red-orange colour, and is sufficiently stable to undergo reactions with various electrophiles including (i) substitution with alkyl halides, Me_3SiCl, Me_3SnCl,[15] Ph_2S_2 and Ph_2Se_2,[13] (ii) addition to aldehydes, carbon dioxide,[15] and pyrylium salts,[16] and (iii) condensation with esters,[17] resulting in benzylic functionalization as seen in **23**. The ability of the *ortho*-alkoxy group to stabilize the toluate anion may be due to a decrease in carbonyl electrophilicity as a result of both steric and electronic effects,[13] with the extended enolate **22** being a likely resonance contributor.[15]

Only recently has a more thorough study of the effect of substitution patterns on the toluate been undertaken. In the course of



Scheme 4. Self-condensation of *ortho*-toluates.