Tetrahedron 66 (2010) 164–171

Contents lists available at ScienceDirect

Tetrahedron

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

Wittig-selectivity in mixed ketones: exploring 1,3-interaction and enolization

Asitanga Ghosh, Indrajit Chakraborty, Nayarussery N. Adarsh, Saswati Lahiri *

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Kolkata 700032, India

ARTICLE INFO

Article history:
Received 17 September 2009
Received in revised form 21 October 2009
Accepted 3 November 2009
Available online 10 November 2009

Keywords:
Mixed ketone
Selective intramolecular olefination
1,3-Interaction

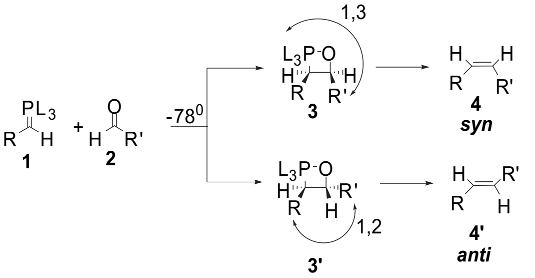
ABSTRACT

The present work explored the primary factors governing regioselectivity of Wittig olefination in bicyclo[2.2.2]oct-5-en-2-ones having 5-aroyl or acyl substitutions. In absence of steric congestion less enolizable ketone kinetically favored the initial formation of the oxaphosphetane ring whereas, in presence of 1,3-interaction between phosphonium ylide and ketone substitutions could switch over the selectivity in other direction.

1. Introduction

The Wittig reaction occupies a position of central importance in organic syntheses since it can convert a carbonyl group to a double bond with high level of geometrical control.[1,2] Extensive work on reaction mechanism using triphenylphosphonium ylides has shown presence of Li-ion containing salts and stability of the intermediate ylide determine the ratio of formation of resultant *Z* and *E*-alkenes.[3] A detailed analysis of the transition state energies for Wittig reactions of aldehydes under salt-free condition provided support for, (i) involvement of oxaphosphetane mechanism and ruled out intervention of any betaine mechanism; (ii) involvement of both the initial addition and the subsequent elimination as key steps in determining *E*/*Z* selectivity; (iii) involvement of primarily 1,2 and 1,3 steric interactions between phosphonium ylides and aldehydes to form a *trans*-planar or, *cis*-puckered transition state which in turn, decide the *E*/*Z* selectivity.[4] Thus, oxaphosphetanes (**3**, **3′**) are formed as the intermediates for these reactions by formal [2+2] cycloaddition (Scheme 1), which then, depending on the nature of interaction, decompose to yield *syn* or *anti* olefin and phosphine oxide.[5]

While detailed work have been reported on mechanism and selectivity of Wittig reactions with aldehydes, such data with ketones are much inadequate.[3a] Furthermore, most of the mechanistic details of carbonyl compounds are generally centered around the correlation of the stabilities of the ylide and the ratio of *E-Z* geometries of the resulting alkenes whereas, in molecules containing more than one carbonyl groups, the selectivity of olefination has not been much looked into. It has been stated that the overall structural details has more influence on the selectivity of Wittig olefination in ketones than in aldehydes.[3a] However, no detailed work on structure-reactivity relationship in molecules with multiple carbonyl groups has yet been reported in the literature. In this present work we tried to bridge this gap using molecules containing enolizable cyclic ketone as well as an acyclic ketone which, depending on the attached substituent may or may not enolize.



Scheme 1. A general Wittig reaction of an aldehyde.

2. Results and discussion

For the present work we selected 5-aroyl or acyl derivatives of bicyclo[2.2.2]oct-5-en-2-ones, **5a–l** as the model compounds most of which were prepared following reported procedures.[6] For identifying the primary factors governing regioselectivity in such

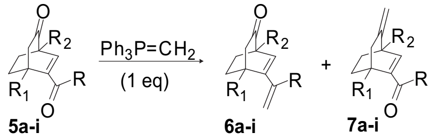
---

* Corresponding author. Tel.: +91 33 2473 4971; fax: +91 33 2473 2805.
E-mail address: ocsl@iacs.res.in (S. Lahiri).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.006

mixed carbonyl compounds Wittig reactions were carried out under the following limiting conditions: (a) the double bond was incorporated in the rigid system to avoid *E-Z* isomerization of the enone; (b) to minimize 1,2-interaction and to avoid the possibility of *E-Z* isomerization in the products, methyltriphenylphosphonium iodide has been used for the present work; (c) to minimize the probability of bis-olefination, 1 equiv of this reagent was slowly added to THF solution of the ketones.

Dropwise addition of triphenyl phosphonium methylide to a THF solution of **5a** under argon atmosphere at low temperature followed by work-up of the reaction mixture after 0.5 h gave **6a** as the exclusive product (Scheme 2). For ketones, risk of enolization is expected to be one of the interfering factors in the initial addition process of oxaphosphetane ring formation. In the present case, as expected, olefination took place selectively at the non-enolizable carbonyl group. When R was replaced by an *iso*-propyl group (**5b**), reactivity of the acyl ketone was substantially reduced due to enhanced enolizability. The less enolizability of the saturated acyl 2-keto group in this case appeared to guide preferential olefination at this carbonyl under the same reaction condition to give **7b** along with minor amount of the other olefin **6b** (Scheme 2). The structures of the products were confirmed from their analytical and spectral data.



where,
a: R=Ph; R$_1$=R$_2$= H b: R=CHMe$_2$; R$_1$=R$_2$= H
c: R=R$_1$=Ph; R$_2$=H d: R=Ph; R$_1$=Me; R$_2$=H
e: R=Ph; R$_1$=OMe; R$_2$=H f: R=Ph; R$_1$=H; R$_2$=Me
g: R=CHMe$_2$;R$_1$=Me;R$_2$=H h: R=R$_1$=Me; R$_2$=H
i: R=Ph; R$_1$=R$_2$=Me

Scheme 2. Wittig reactions of **5a–i**.

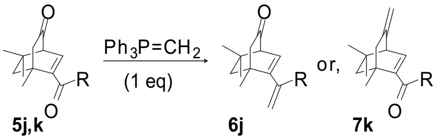
Since steric hindrance in the reactants is also known to complicate Wittig reactions of ketones[3a,7] we wished to compare its effect with that of enolization. When the reaction was carried out with **5c–e**, enolizable 2-keto group was found to be preferentially olefinated giving **7c–e** as exclusive/major products (Scheme 2, Table 1). Similarly, in the case of **5f** the only product obtained was **6f**. In all cases 1,3-interaction between the carbonyl substituents and phenyl ring of the PPh$_3$ ylide appeared to guide the preferential regioselectivity of initial oxaphosphetane ring formation.

Table 1
Yields from Wittig reactions of **5a–i**

Entry	R	R$_1$	R$_2$	5 (%) (Rec)	6 (%)	7 (%)
a	Ph	H	H	9	78	—
b	CHMe$_2$	H	H	5	15	74
c	Ph	Ph	H	21	—	73
d	Ph	Me	H	15	—	79
e	Ph	OMe	H	23	9	62
f	Ph	H	Me	18	76	—
g	CHMe$_2$	Me	H	38	—	58
h	Me	Me	H	—	46	52
i	Ph	Me	Me	46	41	11

That the steric factor often plays a more dominant role than the enolizability of the ketone in this initial step was evident from the reaction of **5g** where the olefination was totally retarded at the acyclic ketone and **7g** became the sole product. On the other hand, replacement of the *iso*-propyl group by a methyl resulted in reduction of steric congestion in **5h** yielding a 1:1 mixture of **6h** and **7h**. In the case of **5i** where both types of carbonyl experienced similar steric congestion, the nonenolizable acyclic ketone was preferentially olefinated to give **6i** and **7i** in 4:1 ratio however, the reaction became much sluggish here (Table 1).

Depending on the molecular framework, even a remote substitution can interfere with the initial step of cycloaddition, Thus, although **7d** was the only product from **5d**, from **5j** only product was **6j** with ~40% recovery of the starting material. Reaction with **5k** was found to be an extremely unfavorable one and 67% of the starting material was recovered from the reaction with **7k** in only 29% yield (Scheme 3, Table 2).

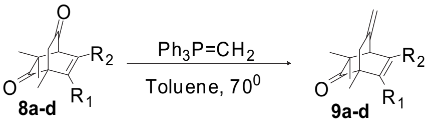


Scheme 3. Wittig reactions of **5j–k**.

Table 2
Yields from Wittig reactions of **5j** and **5k**

Entry	R	5(Rec) (%)	6 (%)	7 (%)
j	Ph	40	48	—
k	CHMe$_2$	67	—	29

The effect of steric congestion also explains the reported selective olefination of **8a–d** where the enolizable but less sterically crowded cyclic ketone took part in the olefination (Scheme 4).[8]



where, **a:** R$_1$=CO$_2$Et; R$_2$=H; 42%
b: R$_1$=R$_2$=CO$_2$Me; 25%
c: R$_1$=Ph; R$_2$=H; 90%
d: R$_1$=R$_2$=Ph; 96%

Scheme 4. Selective Wittig reaction of **8a–d**.

In Wittig reaction, enhanced electronic and steric 1,3-intractions between the ketone substituents and the phenyl groups attached to phosphorous atom tend to destabilize the first step of cycloaddition and puckering of the transition structure is expected to decrease this destabilizing effect specially for non-stabilized ylides.[4,5] From all the examples it appeared the first step of oxaphophetane formation is kinetically guided by these two effects. This was evident from the observations that while **5l**[9] under similar reaction condition exclusively yielded **7l** with 12% recovery of the starting material, use of excess of the ylide now olefinated the sterically congested acyclic ketone to give **10** (Scheme 5). Also, when the cyclic ketone was protected, the ketal **11**[10] under similar condition yielded the olefin **12** in 85% yields.

Since betaines are reported to be stabilized in presence of strong co-ordinating ions like Li-salt[11] we wished to compare our results under Li-free condition to understand if betaines are involved in these reactions. The base used for this purpose was potassium t-butoxide and the product **7d** obtained from **5d** was 76% ,which was