Tetrahedron Letters 50 (2009) 2487-2489

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of 3-alkylidene-piperidin-4-ones via one-pot cascade transylidation-olefination

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ARTICLE INFO

Article history: Received 5 February 2009 Revised 3 March 2009 Accepted 6 March 2009 Available online 11 March 2009

ABSTRACT

3-Alkylidene-piperidin-4-ones with diverse C-5 substitution patterns are synthesized via a one-pot cascade transylidation–olefination sequence. Tributylphosphorus ylides show distinct higher reactivity as compared to triphenyl analogs. *t*-Butanol is the solvent of choice for transylidation, while the Wittig olefination of aliphatic aldehydes requires MeCN as the solvent.

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 α -Alkylidene cycloketone is the structural feature present in many biologically active compounds which exhibited promising antibacterial and antitumor activities.¹ In addition, these α_{β} unsaturated carbonyl compounds are also versatile building blocks in organic synthesis.² Conventional methods for the preparation of this type of compounds relied on Claisen-Schmidt condensation of cycloketones with aldehydes under basic conditions.³ In general, aliphatic aldehydes were not ideal substrates due to multiple side reactions promoted by the base. Bis-condensation was also a serious side-reaction due to the higher reactivity of mono-condensation product.⁴ Recently, catalyzed aldol-dehydration sequences have emerged as alternative approaches with varying degrees of success.⁵ In a different approach, Sato developed an alkyne-based intramolecular nucleophilic acyl substitution reaction using a low valent Ti(II) reagent.⁶ Falck et al. devised an interesting homologation-condensation cascade to construct the exocyclic C-C double bond.⁷ In this connection, classic olefination methods such as Wittig,8 Horner-Wadsworth-Emmons,9 and Julia10 reactions have received little attention, probably due to the difficulty in preparing the corresponding ylids or sulfones, and the intrinsic low reactivity of these species. Only limited examples have been reported, where the substrate was restricted to the most reactive formaldehyde and aromatic aldehydes.¹¹ It should also be mentioned that highly functionalized ylides, especially those β -hetero-substituted, are rare due to possible β-elimination. As a part of our continuing project in the synthesis of nitrogen heterocycles, particularly substituted piperidines,¹² herein we describe our study on the one-pot cascade transylidation-olefination protocol for the synthesis of 3alkylidene-piperidin-4-ones with a general scope.

To begin with, a β -amino-alkylbromide (**2**) was conveniently prepared from the corresponding alcohol **1** by routine Finkelstein reaction (Scheme 1). Compound **2** was sufficiently stable, albeit its structure was considered quite labile owing to the anchimeric

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Scheme 1. Preparation of phosphonium salts and the effect of P-ligands in transylidation.

effect of the adjacent amino group. The phosphonium salts of interest (**3a–c**) were synthesized in excellent to quantitative yields by reacting tertiary phosphines with **2** in acetonitrile under reflux; however, the analogous arsenium salt 3d was not accessible by this procedure, due to the low nucleophilicity of triphenylarsine. The first step in our cascade, namely the transylidation¹³ of these salts, was investigated next. Due to the presence of the ester functionality, only hindered non-nucleophilic bases could be employed, while *n*-BuLi was precluded. It turned out that the steric factor of the P-substituents played a major role in this process. We were pleased to find that 3a and 3b were smoothly deprotonated and the resulting nonstablized ylides cyclized to afford the corresponding β -keto-ylides **4** using *t*-BuOK as the base in toluene, as judged by ³¹P NMR of the crude reaction mixture. After reacting for 2 h at 60 °C, the original signals of the phosphonium salts were completely replaced by new signals ~3 ppm upfield (Table 1), consistent with the literature value.¹⁴ Notably, this process was not





Table 1		
³¹ P NMR data	for phosphonium salts and ylids ^a	

Phosphonium salt	δ^{31} P (ppm)	Ylid	δ^{31} P (ppm	
3a	+23.7	4a	+20.0	
3b	+30.2	4b	+27.1	

^a NMR recorded in C₆D₆, chemical shifts are relative to 85% H₃PO₄.

interfered by possible β -elimination of amine. On the other hand, although the deprotonation of tricyclohexylphosphonium salt **3c** seemed to occur, the resulting ylide may be too hindered to attack



Scheme 2. Solvent effect in transylidation.



Scheme 3. Solvent and P-ligand effects in Wittig olefination.

В

Table 2

One-pot synthesis of 3-alkylidene-piperidin-4-ones

$R^1 R^2$		$R^1 R^2$
CO ₂ Me	1) t-BuOK, t-BuOH	
n∕ [×] → PBu ₃ Br	2) RCHO, solv, 100°C	Bn
2h E C		o Ŕ

Entry	Phosphonium salt	R ¹ , R ²	R	Solvent	Time ^a (h)	Product	Yield ^b (%
1	3b	Me, Me	2-Pr	MeCN	24	9a	60
2	3b	Me, Me	2-Amyl	DMF	40	9b	58
3	3b	Me, Me	p-MeOC ₆ H ₄	Tol	36	9c	68
4	3b	Me, Me	p-O ₂ NC ₆ H ₄	Tol	12	9d	37
5	3b	Me, Me	p-ClC ₆ H ₄	Tol	12	9e	42
6	5	Me, H	2-Pr	MeCN	20	9f	74
7	5	Me, H	1-Amyl	MeCN	24	9g	33
8	5	Me, H	p-MeOC ₆ H ₄	Tol	12	9h	55
9	5	Me, H	p-O ₂ NC ₆ H ₄	Tol	12	9i	36
10	5	Me, H	p-ClC ₆ H ₄	Tol	8	9j	64
11	6	Н, Н	2-Pr	MeCN	24	9k	68
12	6	Н, Н	p-MeOC ₆ H ₄	Tol	20	91	70

^a Unoptimized reaction time.

^b Isolated yields.

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the ester, thus the desired cyclization did not take place. The effect of base was profound. Treating **3b** with the more hindered bases (NaHMDS or LDA) resulted in complex mixtures, presumably due to preferential deprotonation of the α -H on the butyl, while organic base such as DBU was probably too weak and too bulky for the phosphonium salts.

Subsequently, when this protocol was extended to the homologous **5** and **6** possessing relatively acidic α -H of the ester, an interesting solvent effect was found. In toluene, the initial formation of reactive ylides seemed to be problematic; the characteristic orange to red color was not observed. This can be ascribed to the stronger acidity of the ester α -H compared to that of the phosphonium salt.¹⁵ Additional amounts of the base or higher temperature did not solve the problem, because the enolate of ester was no longer an electrophile and thus unable to react with vlides. Fortuitously, when we accidentally shifted the solvent to *t*-butanol (reflux 24 h), the transvlidation proceeded smoothly. The exact nature of this solvent effect cannot be determined at present, but it may be due to that the widely varied basicity of t-BuOK in these two solvents $[pK_a(Tol) \sim 35, pK_a(t-BuOH) \sim 19]$;¹⁶ and that t-BuOH, a protic solvent, promoted the proton exchange between the ester enolate and phosphonium salt (Scheme 2).

Next, the key step of Wittig olefination of β-keto-ylides 4a,b with aldehydes was examined (Scheme 3). It is known that such cyclic phosphoranes bearing an electron-withdrawing group at α -position were deactivated and showed limited reactivity toward aromatic aldehydes only.^{11a} Indeed, when crude **4a,b** were reacted with 2-methyl-propanal in toluene, virtually no product was detected. In view that Wittig reaction showed marked solvent effect,¹⁷ we turned our attention to polar solvents. To our satisfaction, in acetonitrile or DMF 4b afforded the desired product 9a (~50% yield, 36 h) while 4a was still inert. Other solvents such as THF, CH₂Cl₂, DMSO, and HMPA were all ineffective. The enhanced reactivity of 4b compared to that of 4a is in line with earlier reports of the phosphorus ligand effect for related nonstablized tributylphosphorus vlides.¹⁸ On the other hand, using 0.3 equiv PhCOOH¹⁹ or excess LiBr²⁰ as additives did not further improve the yield. As the boiling point of 2-methyl-propanal (63–65 °C) is even lower than that of the solvent, we then carried out the olefination in a pressure vessel, and the yield increased to 60% after 24 h at 100 °C.²¹ The reactions of **4a**,**b** with aromatic aldehydes were further tested. Interestingly, olefination of tributylphosphorus



Scheme 4. Formal alkylation via hydrogenation of exocyclic alkene.

ylide **4b** with *p*-anisaldehyde can be conducted smoothly in toluene, while triphenylphosphorus ylide **4a**, the aza-analog of those carbocyclic ylides described by House and Babad,^{11a} did not react under the same conditions.

With the optimized conditions in place, the one-pot condensation of **3b/5/6** with various aldehydes was carried out (Table 2). Thanks to the improved nucleophilicity of β -keto-tributylphosphorus ylides, a general substrate scope was achieved. For aliphatic aldehydes, regardless of the boiling points, the olefination should be run in MeCN or DMF in a pressure vessel, while for aromatic electrophiles, this step was run in toluene under normal pressure. Moderate to good yields were obtained in most cases, even for the hindered 2-methyl-hexanal (entry 2), while the yields for 4-nitrobenzaldehyde were lower (entries 4 and 9). When this substrate was added to the ylides, the solution turned into dark green color, probably due to the formation of ketyl radical in the presence of excess base (Cannizzarro reaction).²² Dimerization of the product under basic conditions is another possible cause for the low yields.²³

The utility of this cascade reaction was demonstrated by the synthesis of **10**, a compound which cannot be prepared by conventional ketone α -alkylation due to the steric hindrance imposed by β -branching of the alkylating agents (Scheme 4). Hydrogenation (1 atm H₂/cat. PtO₂/MeOH) of the exocyclic C–C double bond in **9k** afforded the product in 90% yield.

In summary, we have developed a one-pot cascade transylidation-olefination sequence for the synthesis of 3-alkylidene-piperidin-4-ones with diverse C-5 substitution patterns. *tert*-Butanol is the solvent of choice for transylidation of substrates possessing acidic α -protons of the ester. Only tributylphosphorus ylides produced the desired Wittig olefination products due to its higher nucleophilicity, while the triphenylphosphorus analogs were unreactive. Both aliphatic and aromatic aldehydes are suitable substrates; for low-boiling aldehydes, the olefination can be conveniently carried out in a re-sealable pressure vessel. Application of this protocol to the synthesis of bioactive natural products is in progress.

Acknowledgments

The author is indebted to Professor Guo-Qiang Lin for valuable suggestions and generous support. Financial support from the National Natural Science Foundation of China (20602008, 20832005) is gratefully acknowledged.

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- 21. Representative procedures: The dried tributylphosphonium salt (0.65 mmol) was placed in a re-sealable pressure vessel equipped with a side-arm under Ar. To this were added t-BuOH (6 mL) and t-BuOK (0.78 mL of 1.0 M solution in t-BuOH. 0.78 mmol) at rt, and the solution was refluxed for 24 h, cooled, and the volatiles were removed in vacuo. To the residue were added MeCN or Tol (4 mL) and aldehyde (0.73-3.3 mmol), the vessel was sealed and stirred at 100 °C for 8-24 h. After cooling, the reaction was diluted with ether (20 mL) and washed successively with water and brine, dried (Na₂SO₄), concentrated, and purified by silica gel flash column chromatography. Compound 5: ¹H NMR (CDCl₃, 300 MHz) & 7.40-7.20 (m, 5H), 3.85-3.60 (m, 4H), 3.71 (s, 3H), 3.00-2.60 (m, 4H), 2.50-2.40 (m, 1H), 2.36-2.05 (m, 6H), 1.50-1.25 (m, 12H), 1.18 (d, J = 6.6 Hz, 3H), 0.92 (t, J = 7.1 Hz, 9H) ppm. ESI m/z (M–Br) 436.2. Compound 9f: ¹H NMR (CDCl₃, 300 MHz) δ 7.40–7.23 (m, 5H), 6.47 (dt, J = 9.9, 2.1 Hz, 1H), 3.75–3.60 (AB, J_{AB} = 12.9 Hz, 2H), 3.70–3.15 (AB-d, J_{AB} = 14.4 Hz, J = 2.4 Hz, 2H), 2.97 (ddd, J = 10.8, 5.7, 1.5 Hz, 1H), 2.62–2.50 (m, 1H), 2.50–2.35 (m, 1H), 2.33 (dd, J = 1.4, 9.6 Hz, 1H), 1.12 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 3.9 Hz, 3H), 0.99 (d, J = 3.9 Hz, 3H) ppm. ¹³C NMR (CDCl₃, 75 MHz) δ 201.3, 145.7, 137.9, 130.9, 128.8, 128.4, 127.3, 62.3, 57.4, 54.0, 42.9, 27.0, 21.8, 21.7, 14.4. HR-ESI-MS m/z calcd for C17H23NO (M+H+) 258.1858, Found 258.1852. Compound 9j: 1H NMR (CDCl₃, 300 MHz) δ 7.45 (t, J = 1.8 Hz, 1H), 7.40–7.19 (m, 9H), 3.91 (dt, J = 14.7, 1.8 Hz, 1H), 3.72–3.58 (AB, J_{AB} = 13.2 Hz, 2H), 3.51 (dd, J = 14.7, 2.4 Hz, 1H), 2.99 (dd, J = 11.4, 6.0, 2.1 Hz, 1H), 2.70–2.58 (m, 1H), 2.38 (dd, J = 11.4, 9.0 Hz, 1H), 1.15 (d, J = 6.9 Hz, 3H) ppm. ¹³C NMR (CDCl₃, 75 MHz) δ 201.5, 137.7, 134.8, 134.0, 133.7, 133.4, 131.4, 128.8, 128.7, 128.3, 127.3, 62.3, 57.0, 56.1, 43.2. 14.6.
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