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

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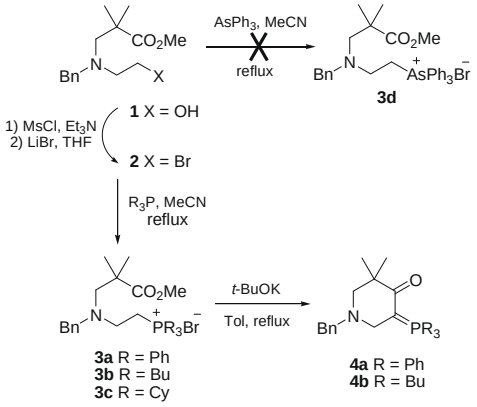
ABSTRACT

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.

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 Julia[10] 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 3-alkylidene-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



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 transylidation[13] 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 ^{31}P 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

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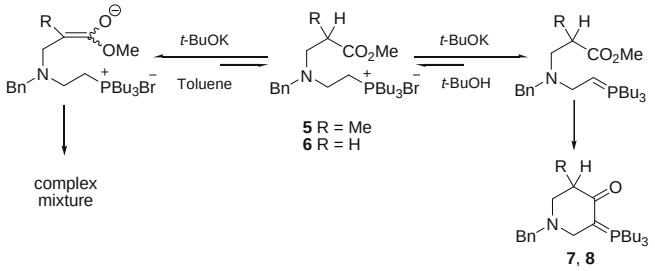
Table 1
^{31}P NMR data for phosphonium salts and ylids[a]

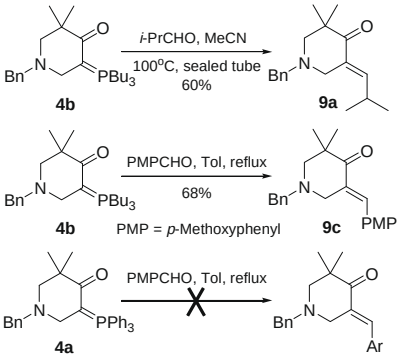
Phosphonium salt	δ ^{31}P (ppm)	Ylid	δ ^{31}P (ppm)
3a	+23.7	**4a**	+20.0
3b	+30.2	**4b**	+27.1

[a] NMR recorded in C_6D_6, chemical shifts are relative to 85% H_3PO_4.

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 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.



Scheme 2. Solvent effect in transylidation.

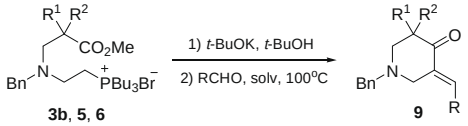


Scheme 3. Solvent and P-ligand effects in Wittig olefination.

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 ylides. Fortuitously, when we accidentally shifted the solvent to *t*-butanol (reflux 24 h), the transylidation 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) ~ 35, pK_a(*t*-BuOH) ~ 19];[16] and that *t*-BuOH, a protic solvent, promoted the proton exchange between the ester enolate and phosphonium salt (Scheme 2).

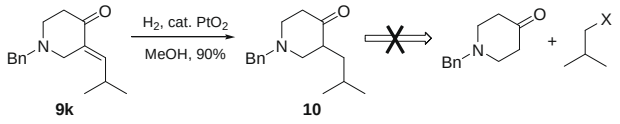
Next, the key step of Wittig olefination of β-keto-ylides **4a**,**b** with aldehydes was examined (Scheme 3). It is known that such cyclic phosphoranes bearing an electron-withdrawing group at α-position were deactivated and showed limited reactivity toward aromatic aldehydes only.[11a] Indeed, when 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, CH_2Cl_2, 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 ylides.[18] On the other hand, using 0.3 equiv PhCOOH[19] or excess LiBr[20] 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

Table 2
One-pot synthesis of 3-alkylidene-piperidin-4-ones



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*-$MeOC_6H_4$	Tol	36	**9c**	68
4	**3b**	Me, Me	*p*-$O_2NC_6H_4$	Tol	12	**9d**	37
5	**3b**	Me, Me	*p*-ClC_6H_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*-$MeOC_6H_4$	Tol	12	**9h**	55
9	**5**	Me, H	*p*-$O_2NC_6H_4$	Tol	12	**9i**	36
10	**5**	Me, H	*p*-ClC_6H_4	Tol	8	**9j**	64
11	**6**	H, H	2-Pr	MeCN	24	**9k**	68
12	**6**	H, H	*p*-$MeOC_6H_4$	Tol	20	**9l**	70

[a] Unoptimized reaction time.
[b] Isolated yields.



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 H_2/cat. PtO_2/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

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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 (Na_2SO_4), concentrated, and purified by silica gel flash column chromatography. *Compound* **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 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**: ^{1}H NMR ($CDCl_3$, 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 = 11.4, 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. ^{13}C NMR ($CDCl_3$, 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 $C_{17}H_{23}NO$ ($M+H^+$) 258.1858, Found 258.1852. *Compound* **9j**: ^{1}H NMR ($CDCl_3$, 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 (ddd, 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. ^{13}C NMR ($CDCl_3$, 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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