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Reinvestigation of synthesis of halo-substituted 3-phenyl-1-(2-pyridyl)-2-propen-1-ones (azachalcones). A tandem reaction for formation of penta-substituted cyclohexanols

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ABSTRACT

A systematic study of the synthesis of halo-substituted azachalcones was conducted. During the reaction course, we obtained not only the target azachalcones, but also penta-substituted cyclohexanols, which are seldom reported in the literatures. The formation of penta-substituted cyclohexanols was dependent on equivalents of base used and reaction time. Their formation followed a tandem reaction: Claisen-Schmidt condensation, three Michael reactions, retro-aldol reaction, and intramolecular aldol cyclization.

1. Introduction

Chalcones are precursors in the synthesis of flavonoids and are found pervasively in natural plants. They exhibit a wide variety of biological activity such as antibacterial,[1] antifungal,[1b] antimalarial,[2] antioxidant,[3] antitumor[4] and antiinflammatory[5] properties. Chalcones possess a 1,3-diphenyl-2*E*-propene-1-one framework (Fig. 1). The most common and widely used strategy in synthesis of chalcones or their analogues is Claisen-Schmidt condensation.

Another non-naturally occurring chalcone-like family is the azachalcones in which annular carbons in either the A or B ring are replaced by nitrogen atom(s) (Fig. 1). Azachalcones exhibit biological properties similar to those of chalcones.[6] Further, they have been used in studies of asymmetric Diels-Alder reactions.[7] The target azachalcones synthesized in this article are from 2-acetylpyridine with a series of halobenzaldehydes under Claisen-Schmidt condensation. We obtained not only the target azachalcones but also unexpected products. These unexpected products were later confirmed to be unusual penta-substituted cyclohexanols by NMR experiments or X-ray analysis. There have been very few reports that mention these cyclohexanol derivatives.[8] In order to clarify their formation, herein we reinvestigate their syntheses and discuss their formation mechanism.

2. Results and discussion

We synthesized a series of B-ring halo-substituted chalcones for evaluation of their biological activity.[9] The synthesis of azachalcones using Claisen-Schmidt condensation[6a,7d,e,8,10,11] (Scheme 1) can be carried out either under catalytic conditions[8,11] or in the presence of a slightly excess amount of base (1–3 equivalent of NaOH or KOH).[6a,10] Either MeOH or EtOH was used as a solvent. Reaction temperature was kept either at 0 to 10 °C for 2–5 h[7d,e,10d,e] or at room temperature overnight.[6a,10b,c] Some reports describe procedures but without providing yields[6a,10]; others describe procedure whereby the expected azachalcones are obtained at moderate[10f] to high yields.[7d,e,11]

We tried to replicate the above-mentioned conditions using stoichiometric amounts of base; however, we were not able to obtain the expected azachalcones at as high yields as described. Only moderate to low yields were obtained. We therefore carefully surveyed the amounts of base used in the reaction. Initially, the mixture concentration was 0.35 M based on **1** in EtOH and an aqueous 8 M KOH solution (1 equivalent) was used as a base (Table 1, entry 1). Reaction completed within an hour and

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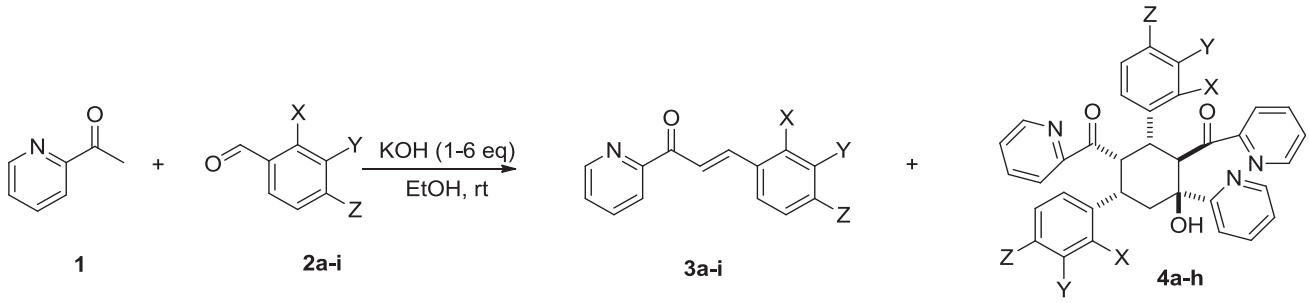
Fig. 1. Representative structures of chalcone and C-2 azachalcone.



a. X=H, Y=H, Z=F **d.** X=H, Y=F, Z=H **g.** X=F, Y=H, Z=H
b. X=H, Y=H, Z=Cl **e.** X=H, Y=Cl, Z=H **h.** X=Cl, Y=H, Z=H
c. X=H, Y=H, Z=Br **f.** X=H, Y=Br, Z=H **i.** X=Br, Y=H, Z=H

Scheme 1. Synthesis of azachaclones **3a-i** and penta-substituted cyclohexanols **4a-h**.

Table 1
Synthesis of 4′-haloazachaclones **3a-c** and penta-substituted cyclohexanols **4a-c**.

Entry	KOH (eq)	3a:4a (%)	Time	3b:4b (%)	Time	3c:4c (%)	Time
1	1	51:0[a]	30 min	35:0[a]	45 min	32:0[a]	1 h
2	1	35:0	4 h	19:0	5 h	12:0	5 h
3	2	57:1[a]	35 min	43:2[a]	40 min	15:6[a]	75 min
4	2	22:3	4 h	21:5	5 h	4:12	5 h
5	4	50:9[a]	15 min	44:4[a]	20 min	15:3[a]	45 min
6	4	9:9	4 h	0:13	5 h	0:23	5 h
7	6	54:4[a]	15 min	41:4[a]	15 min	37:20[a]	15 min
8	6	0:6	4 h	0:11	5 h	0:18	5 h

[a] Isolated yields all based on the complete consumption of **1**.

compounds **3a-c** were obtained at moderate to low yields. We observed longer reaction times to result in much lower yields of **3a-c** (Table 1, entry 2). When two equivalents of base were used, not only chalcone **3a** but also an unexpected penta-substituted cyclohexanol **4a** were obtained (Table 1, entry 3). A structure similar to that of **4a** has been reported as a side product at a low yield (8%) or as a major product during the preparation of 4'-*p*-Tolyl-2,2':6′,2″-terpyridine.[8a] However, neither detailed mechanisms nor procedures have been explicitly described. This penta-substituted cyclohexanol **4a** was well-resolved by NMR spectroscopy. Normally, an equatorial hydrogen is more deshielding than a gemenial axial hydrogen in cyclohexane. However, the opposite result was observed for H_{5a} and H_{5e} of **4a** (Fig. 2), which was probably due to the equatorial hydrogen being in a shielding position on an aromatic ring. Also, the NOESY spectrum observed between H_3 and H_{5a} was as indicated in Fig. 2. The structure of compound **4a** was further confirmed by X-ray crystallography[12] (Fig. 3). We conclude from Table 1 that higher concentrations of base and shorter reaction times produced the target azachalcones at moderate yields (entries 3, 5, 7). Once the reaction time was extended to 4–5 h, the yields of isolated azachalcones dropped dramatically, and the penta-substituted **4a-c** were isolated as major products (Table 1, entries 6, 8).

A plausible mechanism for the formation **4a** is depicted in Fig. 4. Its formation involved tandem Claisen-Schmidt condensation, three Michael reactions (**3a**−**7**), a retro-aldol reaction (**8**) and an intramolecular aldol reaction (**9**).

During the prolonged reaction course, we observed gradually increasing amounts of a polar mixture once the target chalcones were formed (Table 1, *vide infra* Tables 2 and 3). This polar mixture was purified by column chromatography to isolate **4a-h** along with a complex mixture that could not be identified. The unidentified complex mixture was assumed to be a combination of incomplete Michael reaction and uncyclized products which resulted in the low yields of **3a-i** as well as **4a-h**. We do not exclude the possibility of the formation of **4'a-i**[8a] (Fig. 2), however, we were not able to isolate any of these compounds.

The same conditions were applied to synthesis of 3'-haloazachalcones (Table 2). With one equivalent of base and relatively short times, compounds **3d-f** were obtained at moderate to low yields (entry 1). No penta-substituted cyclohexanols were obtained with longer reaction times except **4f** (entry 2). When two or more equivalents of base were used, yields of **3d-f** decreased and **4d-f** increased with longer reaction times (entry 3–8). The results show a similar to that trend in Table 1.

We also studied the 2'-haloazachalcones' synthesis (Table 3). Our observations were consistent with the trends shown in Tables 1 and 2. Yields of **4g** and **4h** increased under extended reaction times with 2, 4, and 6 equivalents base used (entries 4, 6, 8). No penta-substituted cyclohexanol derivative **4i** was formed from condensation between **1** and **2i** even when six equivalents of base were used, probably owing to the larger atom size of bromine in the vicinity of the reaction center restricting cyclization.

In order to test whether the inductive effect might influence the formation of penta-substituted cycloheanol, we replaced the para-halo substituents in B ring with an electron-donating group (OMe, **10**) and reacted under the same conditions as in Scheme 1 (Scheme 2). Compound **11** was received in high yields (87–94%) once compound **1** was completely reacted (Table 4, entries 1, 4, 7, and 10).