A New Lewis Acid System Palladium/TMSCl for Catalytic Aldol Condensation of Aldehydes with Ketones

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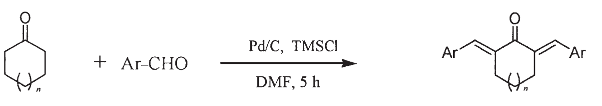
Palladium on charcoal effectively catalyzed the aldol condensation reactions of different ketones with aldehydes in the presence of trimethylsilyl chloride (TMSCl). The following reactions were investigated: (1) aromatic aldehydes with cycloalkanones, (2) aromatic aldehydes with aromatic ketones, (3) cycloalkanones with aliphatic aldehydes, and (4) the self-condensation reactions of aliphatic aldehydes and cycloalkanones.

Reactions forming carbon–carbon bonds, catalyzed by palladium, are very effective tools for synthetic chemists.[1] Aldol condensation is one of the most useful reactions in organic chemistry.[2] In this paper we present a new approach to these condensation reactions where palladium catalyzed the cross and self aldol condensation reactions of ketones with aldehydes in the presence of trimethylsilyl chloride (TMSCl).

Bis(arylmethyllidene)cycloalkanones were a particularly interesting class of compounds which were used as precursors for the synthesis of bis(arylmethyllidene)cycloalkanones with bioactive pyrimidine derivatives[3] and as intermediates to form compounds with particular qualities.[4] Although numerous methods for the preparation of these compounds have been reported,[5–12] some difficulties have been encountered in their actual preparation, because of troublesome procedures, expensive reagents, or poor yields. For example, the classical cross condensation reaction of cycloakanones with aldehydes catalyzed by acids or bases is reversible.[5] Although while Ishii's method gave satisfactory yields, the reagent (Cp_2ZrH_2) was not easily prepared and self-condensation occured as a side reaction.[8] Nakano reported a newer practical method, using Cp_2TiPh_2 as a catalyst and the reaction was carried out at a higher temperature (120 °C) in a sealed ampoule.[9]

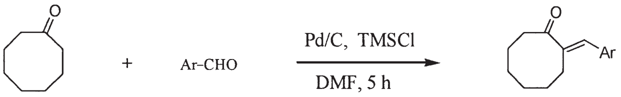
Cyclopentanone (**1a**) and cyclohexanone (**1b**) reacted with different aromatic aldehydes (**2a**–**2h**) such as benzaldehyde (**2a**), 4-methylbenzaldehyde (**2b**), 4-chlorobenzaldehyde (**2c**), anisaldehyde (**2d**), cinnamaldehyde (**2e**), 4-fluoraldehyde (**2f**), 4-nitrobenzaldehyde (**2g**), and furfural (**2h**) with 1–2 mol % of palladium at 75 °C. All the reactions were finished in 5 h with excellent yields and the results of these reactions were shown in Scheme 1. Different attempts to carry out selective mono-condensations of cyclopentanone or cyclohexannone were not successful nor did we obtain a mixture of mono or di-aldol products. Also we did not observe the formation of a self-condensation product of a cycloalkanone in any of these reactions.



$n = 0$	Yield / %	$n=1$	Yield / %
3aa: Ar = C_6H_5	89	3ba: Ar=C_6H_5	91
3ab: Ar = 4-CH_3-C_6H_4	86	3bb: Ar=4-CH_3-C_6H_4	89
3ac: Ar = 4-Cl-C_6H_4	87	3bc: Ar=4-Cl-C_6H_4	85
3ad: Ar = 4-CH_3O-C_6H_4	81	3bd: Ar=4-CH_3O-C_6H_4	83
3ae: Ar = C_6H_5CH=CH	78	3be: Ar=C_6H_5CH=CH	80
3af: Ar = 4-F-C_6H_4	92	3bf: Ar=4-F-C_6H_4	89
3ag: Ar = 4-NO_2-C_6H_4	88	3bg: Ar=4-NO_2-C_6H_4	95
3ah: Ar = C_4H_3O	75	3bh: Ar=C_4H_3O	79

Scheme 1.

In another experiment, when cyclooctanone (**1c**) reacted with different aromatic aldehydes (**2a**–**2h**), contrary to Scheme 1, we obtained neither 2,8-bis(benzylidene)cyclooctanone nor a mixture of mono- with di-aldol products. We only gained a good yield with selective mono-condensation of products (**3ca**–**3ch**) (Scheme 2).



3ca: Ar = C_6H_5 (83%)
3cb: Ar = 4-CH_3-C_6H_4 (78%)
3cc: Ar = 4-Cl-C_6H_4 (80%)
3cd: Ar = 4-CH_3O-C_6H_4 (75%)
3ce: Ar = C_6H_5CH=CH (73%)
3cf: Ar = 4-F-C_6H_4 (82%)
3cg: Ar = 4-NO_2-C_6H_4 (85%)
3ch: Ar = C_4H_3O (70%)

Scheme 2.

The reactions shown in Schemes 1 and 2 were not affected by the substituent groups. Aromatic aldehydes or aromatic ketones carrying either electron-donating substituents such as –CH_3, –Cl, –OCH_3, or electron-withdrawing substituents such as –F, –NO_2 all reacted well, giving excellent yields.

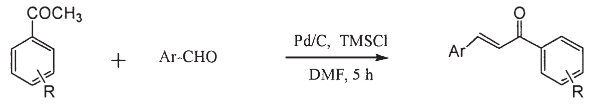
In Scheme 3, cyclopentanne (**1a**) and cyclohexanone (**1b**) reacted with terephthaladehyde (**2i**) at 75 °C, and a yellow polymer was obtained. Despite changing the reaction conditions, such as the temperature (at 20 or 45 °C) and using solvents such as ether, THF, benzene, toluene, chloroform, we did not obtain any 2,2′-terephthalylidene-di-cyclopentanone nor 2,2′-terephthalylidene-di-cyclohexanone. However, cyclooctanone did react with terephthaladehyde (**2i**) through two groups –CHO to form 2,2′-terephthalylidene-di-cyclooctanone (**3ci**) in good yield 79%.

1c

3ci (79%)

Scheme 3.

In the same reaction conditions, aromatic ketones readily reacted with aromatic aldehydes to give a variety of substituted chalcones with excellent yields. These compounds were potentially useful synthetic intermediates as well as having significant pharmacological properties.[13] We studied the condensation of acetophenone (**1d**), 4-nitroacetophenone (**1e**), 3-nitroacetophenone (**1f**), 3-chloroacetophenone (**1g**), 3-methoxyacetophenone (**1h**), and acetic acid 3-acetylphenyl ester (**1i**) with different aromatic aldehydes (**2a**–**2h**). α,β-Unsaturated ketones were isolated and identified with yields ranging between 85 and 98%, no side reaction was observed. Compared to the reactions of 4-substituted acetophenones, 3-substituted acetophenones (**1f**–**1i**) were more difficult.



1d: R = H
1e: R = 4-NO$_2$
1f: R = 3-NO$_2$
1g: R = 3-Cl
1h: R = 3-OCH$_3$
1i: R = 3-OCOCH$_3$

2a: Ar = C$_6$H$_5$
2b: Ar = 4-CH$_3$-C$_6$H$_4$
2c: Ar = 4-Cl-C$_6$H$_4$
2d: Ar = 4-CH$_3$O-C$_6$H$_4$
2e: Ar = C$_6$H$_5$CH=CH
2f: Ar = 4-F-C$_6$H$_4$
2g: Ar = 4-NO$_2$-C$_6$H$_4$
2h: Ar = C$_4$H$_3$O

3da (92 %) 3ea (93 %) 3dg (96 %)
3db (90 %) 3eb (87 %) 3eg (98 %)
3dc (89 %) 3ec (89 %) 3fg (98 %)
3dd (86 %) 3ed (86 %) 3gg (91 %)
3de (89 %) 3ee (85 %) 3hg (88 %)
3df (93 %) 3ef (91 %) 3ig (94 %)
3dh (87 %) 3eh (87 %)

Scheme 4.

In order to investigate this catalytic feature in more details, we researched the cross-condensation between cycloalkanones and aliphatic aldehydes. As reported in the literature,[8] it was difficult to complete the direct cross-condensation reactions. Therefore, this method was an easier and more effective route to prepare 2-alkylidenecycloalkanones. In Scheme 5, during the reaction of cycloalkanones (**1a**–**1c**) with *n*-butylaldehyde (**2j**), valeraldehyde (**2k**), and *n*-heptaldehyde (**2l**), we observed the occurrence of small amounts of self-condensates **3x**–**3z** and **3w** (Scheme 6) as by-products.

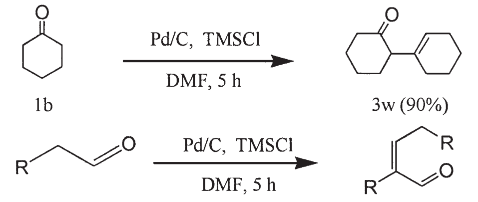
R = *n*-C$_3$H$_7$
3aj: *n* = 0 (58%)
3bj: *n* = 1 (55%)
3cj: *n* = 3 (61%)

R = *n*-C$_4$H$_9$
3ak: *n* = 0 (60%)
3bk: *n* = 1 (68%)
3ck: *n* = 3 (59%)

R = *n*-C$_6$H$_{13}$
3al: *n* = 0 (51%)
3bl: *n* = 1 (63%)
3cl: *n* = 3 (65%)

Scheme 5.

We have extended the usefulness of this catalytic method in the successful self-condensation reactions of cycloalkanones and aliphatic aldehydes (Scheme 6). Self-condensation of cyclohexanone (**1b**) gave excellent yields. Also aliphatic aldehydes (**2j**–**2l**) self-condensed with the dehydrated products of α,β-unsaturated aldehydes (**3x**–**3z**). However we have not obtained the corresponding self-condensed compounds for other cycloalkanones such as cyclopentanone (**1a**) or cyclooctanone (**1c**).



1b

3w (90%)

2j: R = C$_2$H$_5$
2k: R = C$_3$H$_7$
2l: R = *n*-C$_5$H$_{11}$

3x: R = C$_2$H$_5$ (67%)
3y: R = C$_3$H$_7$ (71%)
3z: R = *n*-C$_5$H$_{11}$ (60%)

Scheme 6.

TMSCl exhibited remarkable reactivity as a ‘hardsoft’ reagent. Reagents and all solvents were analytically pure grade and were used without further purification. Cycloalkanones, aldehydes, DMF, and palladium were mixed in flask and TMSCl was added dropwise at room temperature. After 30 min, the reaction mixture was stirred at 75 °C for 4.5 h. The product (**3aa**–**3ig**) precipitated directly after the whole reaction mixture were placed in a refrigerator for over night, filtered through a Buechner funnel, washed with ethanol, and dried to give the target compounds as a crystalloid. Otherwise the reaction mixture was extracted with ethyl acetate; the organic layers were washed with water, dried, filtered off and then evaporated to the compounds (**3aj**–**3cl**, **3w**–**3z**).

In conclusion, we have used palladium as a highly effective catalyst for the cross and self-condensation reactions of aldehydes with ketones shown in Schemes 1–6. Our method offers several advantages, including mild reaction conditions, higher yields, shorter reaction time and a simpler experimental procedure.

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