Tetrahedron Letters 54 (2013) 402–405

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

An efficient C–C bond formation reaction for the synthesis of α-arylated ketones under mild conditions

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ARTICLE INFO

Article history:
Received 19 June 2012
Revised 29 October 2012
Accepted 6 November 2012
Available online 20 November 2012

Keywords:
α-Arylated ketones
Truce Smiles rearrangement
C–C bond formation
Mild reaction condition

ABSTRACT

A wide range of substituted α-arylated ketones were synthesized in moderate to excellent yields via a Truce Smiles rearrangement. The main scaffold has various applications in medical and biochemical fields. This process also provides a facile and direct method for the C–C bond formation.

Introduction

The α-arylated ketones are important components of many natural products, synthetic intermediates, and precursors of natural analogues such as Coumestan,[1] Phenylbenzofurans,[2] and Isoflavones (Fig. 1).[3] Therefore, many synthetic approaches have been reported to construct these scaffolds, including the Friedel–Crafts reaction of phenols with various phenylacetic acids in BF_3–Et_2O,[4] the palladium-catalyzed α-arylation of ketones and esters,[5] (*N*-heterocyclic carbene)-Pd-catalyzed anaerobic oxidation of secondary alcohols and domino oxidation-arylation reactions,[5] the Grignard reaction of benzamides with benzylmagnesium halides,[6] and nickel catalyzed electrosynthesis of ketones from organic halides and iron pentacarbonyl.[7] However, most of the procedures use metal

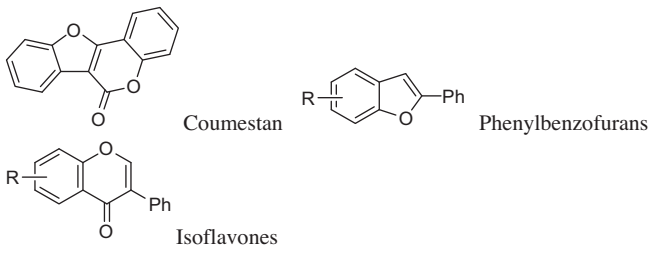
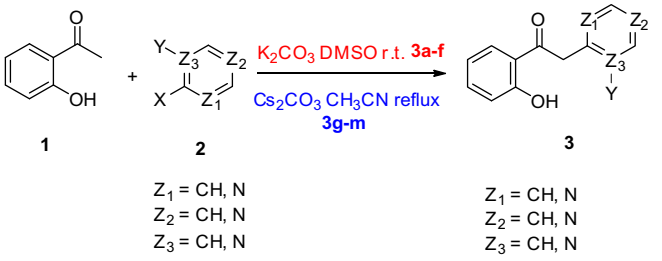
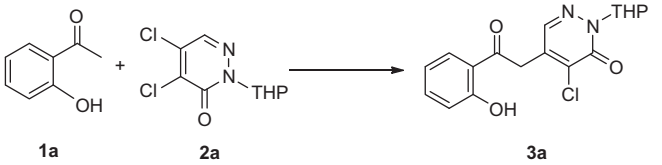


Figure 1. Structure of coumestan, phenylbenzofuran, and isoflavones.



Scheme 1. Synthesis of substituted α-arylated ketones.

Table 1
Optimization of the reaction conditions



Entry	Base	Solvent	Temp/°C	Time/h	Yield/%
1	K_2CO_3	DMF	120	0.8	58
2	Cs_2CO_3	DMF	120	0.9	52
3	NaH	DMF	120	1.2	41
4	K_2CO_3	DMF	rt	21	77
5	K_2CO_3	DMSO	rt	20	97
6	Cs_2CO_3	DMSO	rt	20	84
7	K_2CO_3	DMF	80	4	76
8	K_2CO_3	DMSO	80	4	68
9	Cs_2CO_3	DMSO	80	4	62
10	K_2CO_3	CH_3CN	80	30	89
11	Cs_2CO_3	CH_3CN	80	23	93

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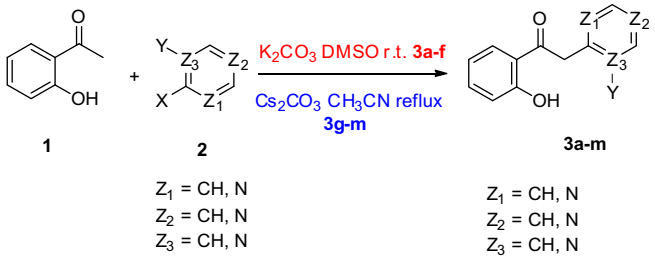
http://dx.doi.org/10.1016/j.tetlet.2012.11.024

Table 2
Synthesis of a variety of α-arylated ketones[10]



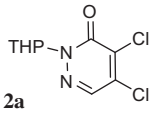
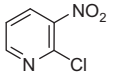
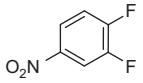
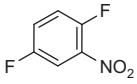
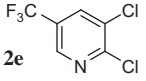
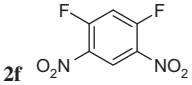
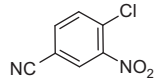
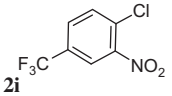
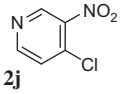
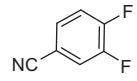
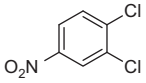
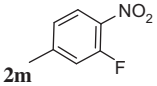
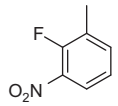
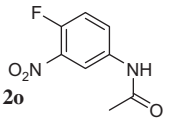
Entry	2a–m	Base	Solvent	Time/h	Yield/%
1	 2a	K_2CO_3	DMSO	14.5	97
2	 2b	K_2CO_3	DMSO	4	69
3	 2c	K_2CO_3	DMSO	17	88
4	 2d	K_2CO_3	DMSO	23	65
5	 2e	K_2CO_3	DMSO	1	84
6	 2f	K_2CO_3	DMSO	11	64
7	 2g	Cs_2CO_3	CH_3CN	6	70
8	 2h	Cs_2CO_3	CH_3CN	5	50
9	 2i	Cs_2CO_3	CH_3CN	4	77
10	 2j	Cs_2CO_3	CH_3CN	1	91
11	 2k	Cs_2CO_3	CH_3CN	1	63
12	 2l	Cs_2CO_3	CH_3CN	9	50
13	 2m	Cs_2CO_3	CH_3CN	8	55

Table 2 (*continued*)

Entry	2a–m	Base	Solvent	Time/h	Yield/%
14	 2n	Cs_2CO_3	CH_3CN	10	Not detected
15	 2o	Cs_2CO_3	CH_3CN	8	Not detected

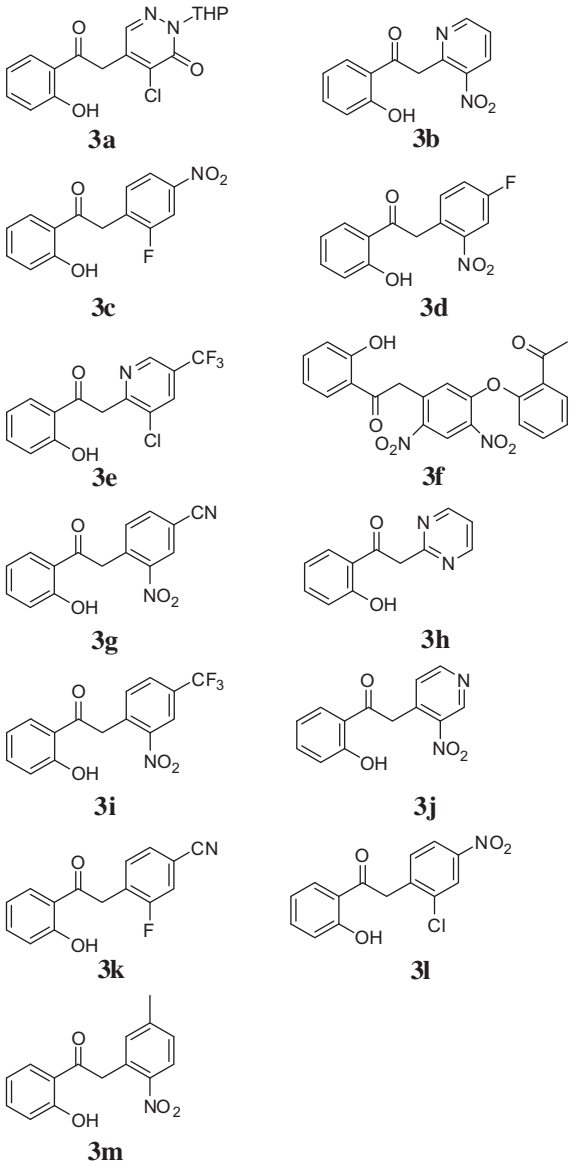
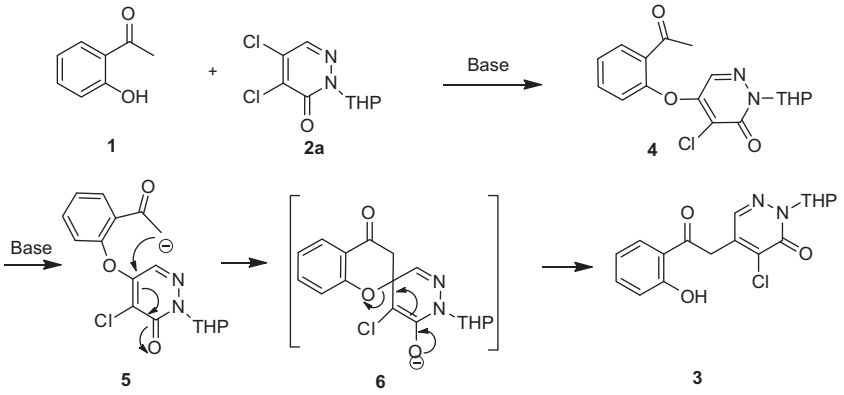


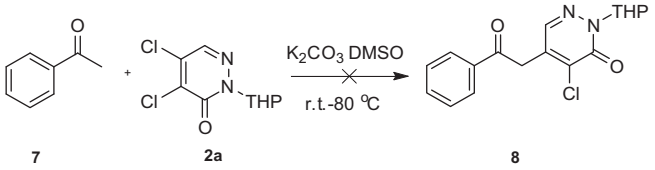
Figure 2. Structures of desired compounds **3a–m.**

catalysts or the Grignard reagent, which is not eco-friendly or sensitive to air and moisture.

Truce Smiles rearrangement has become a powerful and flexible method in pharmaceutical, biomedical, and optical chemistry.[8]



Scheme 2. A plausible reaction mechanism.



Scheme 3. An evidence on the Truce Smiles rearrangement.

Recently, our lab has reported the synthesis of several different kinds of heterocyclic compounds via the Smiles rearrangement.[9]

Herein, we report an efficient C–C bond formation reaction for the synthesis of a variety of substituted α-arylated ketones using readily available 1-(2-hydroxyphenyl)ethanone and substituted benzenes or pyridines via a Truce Smiles rearrangement (Scheme 1).

Results and discussion

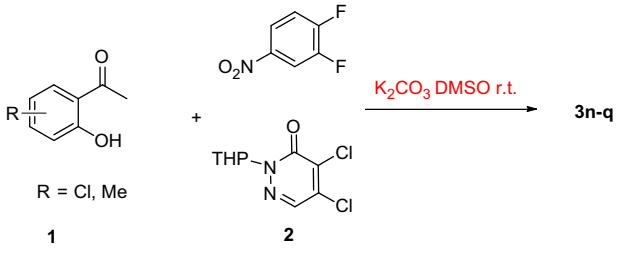
At first, **2a** and **1** were chosen as the starting materials to optimize the reaction conditions including bases and solvents. As shown in Table 1, it is interesting to find that K_2CO_3 was the most suitable base while DMSO was the best solvent, affording the desired product in 97% yield (Table 1, entry 6). The following investment on the condition suggested Cs_2CO_3–CH_3CN system also performed well in this case (entry 11).

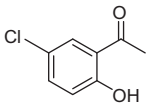
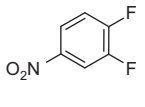
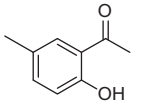
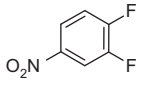
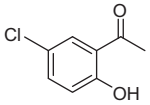
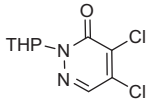
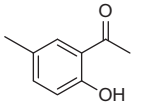
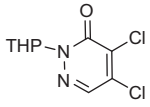
Under the optimized reaction conditions, we investigated the scope of the substituted benzenes **2**. The reaction of **2a–e** with **1** gave the corresponding products in good to excellent yields from 65–97% (Table 2, entries 1–5). However, the reaction of **2f** with **1** did not proceed as the route we thought, instead, **3f** was observed as the sole product (Table 2, entry 6).

In order to shorten the reaction time, we treated **1** with **2g–m** in the presence of Cs_2CO_3 in CH_3CN at reflux temperature, and the corresponding products were obtained in moderate to excellent yields (Table 2, entries 7–13). We note that the methodology has better tolerance to substrate with electron-withdrawing group. We have examined several examples with electron-donating group, but only 2-fluoro-4-methyl-1-nitrobenzene could lead to the desired product. Obviously a substrate with electron-withdrawing group performed better. The structures of desired compounds were shown in Figure 2.

The plausible mechanism was presented in Scheme 2. **1** reacted with **2a** to give **4**, which then underwent the Smiles rearrangement, affording the desired product **3**. The reaction of acetophenone with **2** did not occur even when the temperature was up to

Table 3
Exploration to the scope of the methodology



Entry	Substrate **1**	Substrate **2**	Time/h	Yields/%
1			10	81
2			8	82
3			18	71
4			15	79

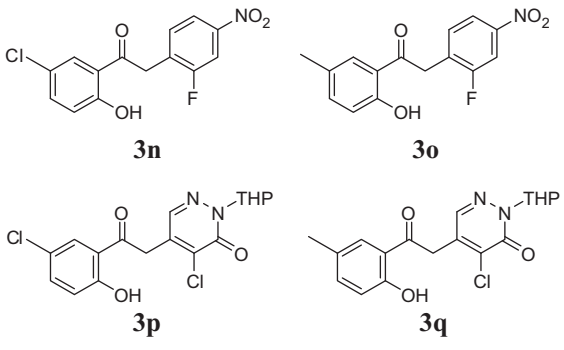


Figure 3. Structures of desired compounds **3n–q**.

80 °C, which indicated that the reaction did proceed via the Truce Smiles rearrangement (Scheme 3).

To explore the scope of the methodology, we employed 1-(5-chloro-2-hydroxyphenyl)ethanone and 1-(2-hydroxy-5-methylphenyl)ethanone as substrates. The result was listed in Table 3 and Figure 3. We are pleased to find the remarkable tolerance for the substrates to benzene and heterocyclic compound with the yields ranging from 71% to 82%.

Conclusion

In conclusion, a variety of functionalized α-arylated ketones were systematically obtained in moderate to excellent yields via the Truce Smiles rearrangement under mild conditions. This C–C bond formation method for the construction of the α-arylated ketones has wide applications in medicinal chemistry.

Acknowledgment

We are grateful to the National Science Foundation of China (No. 21172131), IIFSDU (No. 2010TS052), and the State Key Laboratory of Natural and Biomimetic Drugs of Peking University (K20090205) for financial support of this research.

Supplementary data

Supplementary data (representative experimental procedures and spectral data of compounds **3a–q** are detailed.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.024.

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10. *A typical synthetic process and characterization data (NMR and MS)*: To a solution of 1-(2-hydroxyphenyl)ethanone (150 mg, 1.1 mmol) in DMSO (10 mL) were added 1,2-difluoro-4-nitrobenzene (150 mg, 0.92 mmol) and K_2CO_3 (380 mg, 2.76 mmol), then the mixture was stirred for 17 h at room temperature, and then H_2O (30 mL) was added and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with sat. brine (2 × 20 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (PE/EtOAc = 5:1) to afford the desired product **3c** as a yellow solid (222 mg, 88%). ^{1}H NMR (100 MHz, $CDCl_3$) δ 11.84 (s, 1H), 8.05–8.08 (dd, 1H, J = 1.92, 8.36 Hz), 7.99–8.02 (dd, 1H, J = 2.2, 9.24 Hz), 7.85–7.88 (dd, 1H, J = 1.4, 8.04 Hz), 7.52–7.56 (m, 1H), 7.44–7.48 (m, 1H), 7.26 (s, 1H), 7.02–7.04 (dd, 1H, J = 0.6, 8.4 Hz). 6.96–7.00 (m, 1H), 4.48 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 162.7, 162.2, 158.9, 137.2, 132.5, 132.5, 129.7, 129.1, 128.9, 119.4, 119.3, 118.9, 118.7, 115.5, 111.2, 38.4. HRMS Calcd for $C_{14}H_{10}FNO_4$, 275.0594. Found, 275.0667.