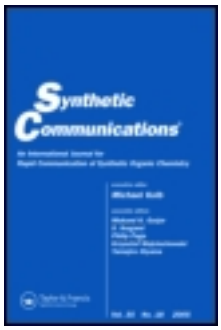

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Trifluoroacetic Acid-Catalyzed Synthesis of N-(1-(3-chlorophenyl) -3-aryl-3-oxopropyl)-2-(4-nitrophenyl) acetamides via Dakin-West Reaction

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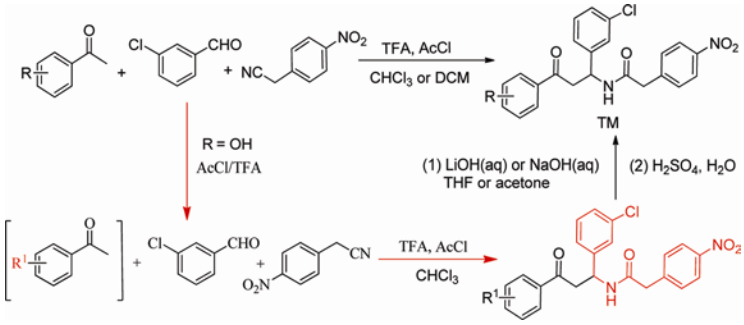
Abstract

A series of novel *N*-(1-(3-chlorophenyl)-3-aryl-3-oxopropyl)-2-(4-nitrophenyl) acetamides were synthesized using *p*-nitrophenylacetonitrile, *m*-chlorobenzaldehyde and aryl methyl ketones as starting materials and trifluoroacetic acid (TFA) as catalyst. This for the first time realized an improved Dakin-West reaction in which *p*-nitrophenylacetonitrile was involved. The chemical structures of up to fifteen target molecules were characterized by ^{1}H NMR, ^{13}C NMR, and HR MS. This method provides a facile synthetic protocol under more moderate reaction conditions, smaller dosage (0.40 mol%), and hence lower cost, of catalyst and simpler post-treatment in comparison to other known methods. A reaction mechanism is proposed in which hydroxyacetophenone is first catalytically converted into corresponding acetoxyacetophenone prior to be involved in the subsequent Dakin-West reaction that eventually leads to hydroxyl acetylated target compounds.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



KEYWORDS: Multicomponent reaction, Dakin-West reaction, trifluoroacetic acid, *β*-arylacetamido ketone, *p*-nitrophenyl acetonitrile

INTRODUCTION

One-pot, multicomponent reactions (MCRs) have attracted much attention since it was put forward by Strecker in 1850[1]. MCRs can be used to synthesize complicated and diverse molecules in a very fast, convenient and time-saving manner, and thus become one of the best tools in combinatorial chemistry for establishing appropriate compound libraries[2]. For the above reasons, to some extent, the discovery of novel MCRs and the improvement of known MCRs have become increasingly active research subjects in recent years[3].

Nitrogen-containing molecules are ubiquitous in nature[4]. Among clinical drugs, nitrogen-containing molecules are usually predominant. For example, among the eighteen new chemical entities marketed in 2008, sixteen of which contain nitrogen atom[5]. *β*-Acetamido ketones, one of the nitrogen-containing molecules, are versatile intermediates for the synthesis of important organic molecules like 1,3-amino alcohols[6] present in antibiotic drugs such as nikkomycins or neopolyoxins[7], *β*-amino acids[8] and *γ*-lactams[9]. Moreover, *β*-Acetamido ketones has been reported as a potential *α*-glucosidase inhibitor[10]. Our laboratory has also found that some *β*-acetamido ketones possess antidiabetic activation activities[11]. Thus, any efficient synthetic method of *β*-acetamido ketones is highly desirable.

What makes us very excited is that the improved Dakin-West reaction is not only a MCRs, but also the most convenient method for the synthesis of *β*-acetamido ketones. Currently, studies on the improved Dakin-West reaction mainly focus on the discovery of new catalysts[12] and novel molecules including chiral molecules[13].Our group has found that trifluoroacetic acid (TFA) is an efficient catalyst for the synthesis of *β*-acetamido ketone[14]. However, to our best knowledge, the improved Dakin-West reaction of *p*-nitrophenyl- acetonitrile with aromatic aldehydes and enolizable aryl methyl ketones has not been observed so far. In view of this, we introduced *p*-nitrophenylacetonitrile for the first time into the improved Dakin-West reaction to prepare a series of novel *β*-(*p*-nitrophenyl)acetamido ketones. The synthetic procedure is outlined in ***Scheme 1***.

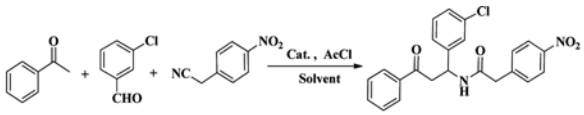
Interestingly, the hydroxyl- containing ketones directly produced the hydroxyl acetylated *β*-acetamido ketones in this one-pot improved Dakin-West reaction, which provides a new way to synthesize this novel kind of compounds.

RESULTS AND DISCUSSION

Currently, acetylation of *β*-amino ketones[15], Mannich-type reaction of acetamides[16], and Michael addition of *α, β*-unsaturated ketones with acetamides[17] are the usual options to synthesize *β*-acetamido ketones. However, the most classical and facile synthetic method is the improved Dakin-West reaction. (One paragraph has been deleted herein)

Recently, the studies of the improved Dakin-West reaction have made remarkable progress, including ketones being extended from simple methyl ketones to cyclic ketones[18], aryl alkyl ketones[19] and *β*-ketoesters[20]. In addition, other nitriles like benzonitrile, phenylacetonitrile, acrylonitrile as well as ethyl cyanoacetate are also reported[19]. An increasingly wider range of catalysts are documented, including Lewis acid[20], proton acid[21], heteropoly acid[22], polymer resin[23] and ZnO nanoparticles[24]. However, the catalysts available for the Dakin-West reaction of benzonitrile or phenylacetonitrile are limited to a small group of species such as $ZrOCl_2 \cdot 8H_2O$[25], $SiCl_4$-$ZnCl_2$[19] or BiOCl[26].

In previous studies[11,14] we identified TFA as an efficient catalyst for some Dakin-West reactions of acetonitile, in the absence of phenylacetonitrile or substituted phenylacetonitrile. In an attempt to extend the application scope of TFA, we embarked on an investigation to the improved Dakin-West reaction of *p*-nitrophenylacetonitrile. Not surprisingly, for a start the reaction of *p*-nitrophenylacetonitrile, aryl methyl ketone, and aromatic aldehyde in the presence of 0.30 mol% TFA did not proceed at any appreciable rate. Therefore we decided to probe the reaction conditions of a model reaction as shown in ***Equation 1*** below.



Equation 1 The model reaction among *p*-nitrophenylacetonitrile, *m*-chlorobenzaldehyde and acetophenone

Effect Of Catalyst On The Model Reaction

It is known that the above mentioned catalysts for the improved Dakin-West reaction generally lead to decent yields. However, these catalysts also suffer serious drawbacks such as significant cost[27], high active temperature[28] and tedious purifications[29]. Consequently, development of efficient, cheap and readily available catalysts for the synthesis of *β*-arylacetamido ketone is highly desirable.

For the above model reaction, no catalyst has been reported till to now. To realize this coupling reaction, a series of candidates were screened, including $SiCl_4$-$ZnCl_2$, $ZrOCl_2 \cdot 8H_2O$, TFA, $FeCl_3 \cdot 6H_2O$, $SnCl_2 \cdot 2H_2O$ and $CeCl_3 \cdot 7H_2O$, with the experimental

results summarized in ***Table 1*** below.

$ZrOCl_2 \cdot 8H_2O$[25] and $SiCl_4$-$ZnCl_2$[19] (entries **1** and **2)** show steady progress as evident by TLC, but the coloration of the reaction system, close to dark brown, seriously hinders the observation and post-treatment of the products. On the other hand, $FeCl_3 \bullet 6H_2O$, $SnCl_2 \bullet 2H_2O$ and $CeCl_3 \bullet 7H_2O$ catalysts (entries **6** ~ **8**) result in fairly low yields, mainly due to abundant by-products. However, in the case of TFA as catalyst, which was pioneered by our group for the improved Dakin-West reaction[11,14], the model reaction achieves the highest yield at TFA loading 0.40 mol% (entry **4**). Considering the smaller dosage, and hence lower cost, of catalyst and simpler post-treatment in comparison to other known methods, we decide to use TFA loading of 0.40 mol% for the improved Dakin-West reaction with *p*-nitrophenylaceto- nitrile, *m*-chlorobenzaldehyde and aryl methyl ketones as starting materials.

Thermal Effect On The Model Reaction

The thermal effect is examined by conducting the model reaction at different temperature. At 30°C in $CHCl_3$, there is no sign of any target product on TLC plate; at 60°C in $CHCl_3$, the point of main product is not obvious. However, at 45°C in $CHCl_3$, and 35°C in DCM, the points of a single product are overwhelming. Consequently the optimal reaction temperature is fixed at 45 in $CHCl_3$ and 35°C in DCM.

Effect Of Solvent On The Model Reaction

For the above model reaction, DCM, THF, CH_3OH, $CHCl_3$, or without using any solvent, are systematically tested. Using CH_3OH as the solvent, there is no point of target product appeared on TLC plate. In THF, or in the case of no solvent, no reaction is observed for up to 100 hours. While in DCM or $CHCl_3$, the main product appears gradually. Therefore all the subsequent reactions are carried out in the presence of 0.40 mol% TFA in DCM at 35 or $CHCl_3$ at 45.

Encouraged by these remarkable results of the model reaction, a variety of acetophenones with electron-withdrawing or -donating substituent(s) are screened to evaluate the scope of substrates in the TFA-catalyzed, multicomponent one-pot reaction. Consequently, a series of *β*-(*p*-nitrophenyl)acetamido ketones are prepared under optimal conditions, and the results are displayed in ***Table 2***.

In the $CHCl_3$ series (**Figure 1**), the reaction using 3,4-dichloroacetophenone as starting material reached a yield over 76%, while that using 4-chloroacetophenone only had a yield of 53.1%, indicating the impact of the number and location of chlorine atom on the yield. For different substitution group at the identical location of acetophenone, the yields are in line with the trend of the electron-withdrawing ability of the substituents, for example, **TM-03** (4-F)>**TM-04** (4-Cl)>**TM-06** (4-Br)>**TM-08** (4-CH_3)>**TM-10** (4-*i*-Bu)>**TM-11** (4-OCH_3); **TM-01** (3-NO_2)>**TM-05** (3-Br); and **TM-02**

(3,4-diCl)>**TM-09** (3,4-diCH_3). However, 4-nitroacetophenone led to no product. On the other hand, for substituents in the *para* position, aromatic ketones with electron-withdrawing groups reacted faster than electron-donating groups. These results highlight the remarkable impact on the final yield by the electron density distribution. It is probable that the electron-withdrawing effect of the substituent made the enolization of carbonyl easier, resulting in the attack of the intermediate formed previously by aldehyde and nitrile more conducive, eventually led to more vigorous reaction.

For the DCM series (**Figure 2**), the yield of the reaction involving double substituted acetophenone by chloro atom tend to be lower than a mono substituted counterpart, for example, **TM-02** (3,4-diCl)<**TM-04** (4-Cl). For different substituent(s) at the identical location of acetophenone, the stronger the electron-withdrawing effect of the substituent(s) on the aromatic ketones, the higher the yield generally. Among them, 3-nitroacetophenone led to an excellent yield of 87.2% in DCM. In contrast to the $CHCl_3$ series, the acetophenones with electron-withdrawing substituent(s) reacted more slowly than that with electron-donating substitutent(s), which showed that the rate of reaction changed along with different solvent, probably due to the difference in solubility and reaction temperature originated from solvent itself. But the strict trend of these reactions in $CHCl_3$ and CH_2Cl_2 does not display sufficiently, the root reason remains unclear to us.

The reaction of hydroxyacetophenone to yield hydroxyl acetylated *β*-acetamido ketones could have taken two drastically different pathway. I.e. either hydroxyacetophenone was initially converted into corresponding acetoxyacetophenone, as catalyzed by TFA, and then participated in the improved Dakin-West reaction which led to hydroxyl acetylated target molecule (**B**); or all reactants initially participated in the improved Dakin-West reaction which afforded the intermediate product (**A**) which was in turn converted into the final target molecules (**B**), as shown in ***Scheme 2***.

Given the fact that existing literatures hardly cover any kinetic insight[30], we diligently designed the following experiments to unravel the plausible reaction pathway:

Procedure **1**. To a solution of hydroxyacetophenone in $CHCl_3$, acetyl chloride was added dropwise, stirred continuously at 15-17 and monitored by TLC.

Procedure **2**. To a solution of hydroxyacetophenone and acetyl chloride in $CHCl_3$, TFA was added dropwise, stirred continuously at 15-17 and monitored by TLC.

Procedure **3**. Conventional one-pot synthesis at 15-17 .

Procedure **4**. To a solution of hydroxyacetophenone and acetyl chloride in $CHCl_3$, TFA was added dropwise. After stirring for 2 hours at 15-17 , *p*-nitrophenylacetonitrile and

m-chlorobenzaldehyde were added sequentially. Then common post-treatment was followed.

Procedure **5**. Instead of hydroxyacetophenone, acetoxyacetophenone (prepared previously by Procedure **5'**) was used as the starting material.

Procedure **5'**. To a solution of hydroxyacetophenone and solid Na_2CO_3 in $CHCl_3$, AcCl was added dropwise in ice bath. After stirring for half an hour, the mixture was stirred at 35 , stirred continuously and monitored by TLC;

Procedure **6**. The resultant hydroxyl acetylated *β*-acetamido ketones were selectively deacetylated in LiOH-H_2O, or NaOH-H_2O in THF, or acetone to yield the corresponding deacetylated products.

In procedure **1**, hydroxyacetophenone reacted with acetyl chloride to ultimately produce acetoxyacetophenone over a period of several hours, evident of sluggish reaction rate in the absence of an effective catalyst. However in procedure **2** where TFA was present, significant acetoxyacetophenone formed within one hour, indicating that TFA greatly accelerate the formation of acetoxyacetophenone.

In procedure **4**, a new spot emerged within 4 hours on TLC plate, identical to the new

substance generated by procedures **3** and **5**. In the same time frame, hydroxyacetophenone remained in procedure **2** but almost completely disappeared in procedure **4**; in comparison, acetoxyacetophenone remained in procedure **2** and **4**, indicating a promotion effect of the conversion of hydroxyacetophenoneone into acetoxyacetophenone. These experimental results uncovered important mechanistic insight in that hydroxyacetophenone is first converted into acetoxyacetophenone which then subsequently leads to acetylated *β*-acetamido ketones in the improved Dakin-West reaction.

In procedures **3**-**5**, the reaction time was sequentially reduced corresponding to increased yield, suggesting acetoxyacetophenone being a more favorable reactant than hydroxyaceto -phenone. Also the mutual promotion between acetylation and the Dakin-West reaction process made procedure **4** faster than procedure **3**, which also confirm the aforementioned hypothesis.

The experimental results show that the yield of the reaction participated by *m*-hydroxy-acetophenone is higher than that of *p*-hydroxyacetophenone, that is, **TM-12**> **TM-13**. For deacetylation reaction, **TM-13** is easier than **TM-12**, as the later requires stronger base and takes longer time to complete, which proves that meta-acetylated product is more stable, easier to generate, and hence the higher yield.

On the basis of all the above results, we propose the mechanism as follows in ***Figure 3*.** The presence of acetyl chloride is necessary for the transformation and the reactions in its absence give lower yield or even none of the desired product even after several hours.

In conclusions, this research presents TFA as an efficient catalyst for the improved Dakin-West reaction involving *m*-chlorobenzaldehyde, *p*-nitrobenzeneacetonitrile and aryl methyl ketones as starting materials, that produce *N*-(1-(3-chlorophenyl)-3-aryl-3-oxopropyl) -2-(4-nitrophenyl)acetamides. This investigation for the first time establishes the reaction pathway of hydroxyacetophenone, in which TFA initially catalyzes the conversion of hydroxyacetophenone into corresponding acetoxyacetophenone, followed by the Dakin-West reaction that eventually leads to hydroxyl acetylated target compounds. This study has also expanded the application scope of TFA and laid the foundation for further research on the Dakin-West reaction with *p*-nitrophenylacetonitrile.

EXPERIMENTAL

General Procedure For The Synthesis Of *B*-Arylacetamido Ketones

To a solution of *p*-nitrophenylacetonitrile (1.0 mmol), *m*-chlorobenzaldehyde (1.2 mmol) and acetyl chloride (0.4 mL) in $CHCl_3$ (3 mL), TFA (0.40 mol%) was added dropwise in ice bath. After half an hour, aromatic ketone (1.2 mmol) was added into the mixture at a controlled temperature of 45 . The progress of the reaction was monitored by TLC. On

completion, ice water (5 mL) was poured into the reaction mixture and stirred thoroughly before the solution was adjusted to pH 7 with saturated $NaHCO_3$. Subsequently, the reaction mixture was extracted with DCM. The organic layer was dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure. The crude product obtained was recrystallized from a mixture of ethyl acetate/petroleum (ratio of volume, 1/3) or in methanol to afford the pure product.

Reasoning Experiments Of Reaction Process

Procedure **1**. To a solution of hydroxyacetophenone (1.0 mmol) in $CHCl_3$ (1 mL), acetyl chloride (0.4 mL) was added dropwise, stirred continuously at 15-17 and monitored by TLC.

Procedure **2**. To a solution of hydroxyacetophenone (1.0 mmol) and acetyl chloride (0.4 mL) in $CHCl_3$ (1 mL), TFA (0.40 mol%) was added dropwise, stirred continuously at 15-17 and monitored by TLC.

Procedure **3**. To a solution of *p*-nitrophenylacetonitrile (1.0 mmol), *m*-chlorobenzaldehyde (1.2 mmol) and acetyl chloride (0.4 mL) in $CHCl_3$ (3 mL), TFA (0.40 mol%) was added dropwise in ice bath. After half an hour, hydroxyacetophenone (1.0 mmol) was added into the mixture at 45 . The progress of the reaction was monitored by TLC. On completion, ice water (5 mL) was poured into the reaction mixture and

stirred thoroughly before the solution was adjusted to pH 7 with saturated $NaHCO_3$. Subsequently, the reaction mixture was extracted with DCM. The organic layer was dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure. The crude product obtained was recrystallized from a mixture of ethyl acetate/petroleum (ratio of volume, 1/3) or in methanol to afford the pure product.

Procedure **4**. To a solution of hydroxyacetophenone (1.0 mmol), and acetyl chloride (0.4 mL) in $CHCl_3$ (3 mL), TFA (0.40 mol%) was added dropwise in ice bath. After two hours, *p*-nitrophenylacetonitrile (1.1 mmol), *m*-chlorobenzaldehyde (1.5 mmol) were added into the mixture at 45 . The progress of the reaction was monitored by TLC. On completion, the post-treatment was the same as Procedure **3**.

Procedure **5**. Instead of hydroxyacetophenone, acetoxyacetophenone was used as the starting material, then common operation was followed as Procedure **3**.

Procedure **5'**. To a solution of hydroxyacetophenone (1.0 mmol) and solid Na_2CO_3 (0.6 mmol) in $CHCl_3$ (1 mL), AcCl (0.4 mL) was added dropwise in ice bath. 30 min later, the mixture was stirred at 35 . The progress of the reaction was monitored by TLC. On completion, filtered, and the filtrate was evaporated under reduced pressure to give oil, which was used directly in the subsequent Dakin-West reaction.

Procedure **6**. To a solution of the product **12** or **13** (1.0 mmol) in acetone or THF (3 mL), 1 *N* LiOH-H_2O or NaOH-H_2O (4 mL) was added dropwise in ice bath. Subsequently, the reaction mixture was stirred at ambient temperature (16-20) and the progress of the reaction was monitored by TLC. On completion, the reaction mixture was evaporated under reduced pressure. After the removal of the solvent, the solution was adjusted to pH 3-4 with 2 N H_2SO_4 in ice bath, instantaneous precipitation of a lot of yellow solid which was filtered, and the filter cake was washed with water (1 mL×3) to afford the pure product.

Spectral Data For *N*-(1-(3-Chlorophenyl)-3-Oxo-3-Phenylpropyl)-2-(4-Nitrophenyl) Acetamide (TM-07)

Yellowy powder; yield: 43.4% (in $CHCl_3$) and 66.2% (in DCM).

^{1}H NMR (600 MHz, DMSO-d_6): δ 3.44-3.64 (m, 4H, $COCH_2CH$ and $NHCOCH_2$), 5.34-5.38 (m, 1H, CHN), 7.28-7.34 (m, 3H, Ar-H), 7.38 (s, 1H, Ar-H), 7.48 (d, J = 9.00 Hz, 2H, Ar-H), 7.53 (t, J = 7.80 Hz, 2H, Ar-H), 7.65 (t, J = 7.80 Hz, 1H, Ar-H), 7.97 (d, J = 7.80 Hz, 2H, Ar-H), 8.15 (d, J = 8.40 Hz, 2H, Ar-H), 8.72 (d, J = 7.20 Hz, 1H, NH) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 196.8, 168.3, 146.2, 145.3, 144.3, 136.4, 133.4, 133.0, 130.3, 130.2, 128.7, 128.1, 126.9, 126.4, 125.4, 123.3, 48.8, 44.2, 41.9 ppm. HR MS calcd for $C_{23}H_{19}ClN_2O_4Na$ 445.0931, found 445.0924.

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SUPPLEMENTARY CONTENT

Supporting Information: full experimental detail, ^{1}H and ^{13}C NMR spectra, and HR MS are available online.

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Table 1. Effect of catalysts on the model reaction[a]

Entry	Catalyst	Amount (mol%)	Yield [b] (%)
1	$SiCl_4$-$ZnCl_2$	5.0	38.4
2	$ZrOCl_2 \cdot 8H_2O$	20.0	56.4
3	TFA	0.30	<10
4	TFA	0.40	66.4
5	TFA	0.50	58.5
6	$FeCl_3 \cdot 6H_2O$	10.0	18.5
7	$SnCl_2 \cdot 2H_2O$	20.0	8.5
8	$CeCl_3 \cdot 7H_2O$	10.0	23.9

[a] The reactions were performed in CH_2Cl_2 at 35 for 24 h, aided by AcCl (0.4 mL), and in the following amount: *p*-nitrophenylacetonitrile (0.5 mmol), *m*-chlorobenzaldehyde (0.6 mmol), and acetophenone (0.6 mmol).

[b] Isolated yield based on *p*-nitrophenylacetonitrile.

Table 2. Experimental results under optimal conditions[a]

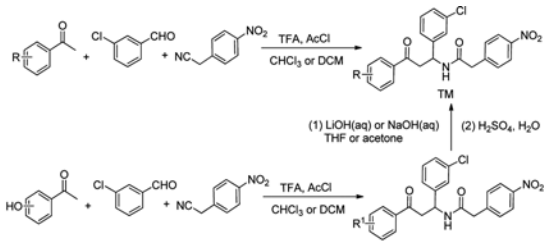
Compd.	R	Time (h)		Yield (%)		m. p. ( )
		$CHCl_3$[b]	DCM[c]	$CHCl_3$[b]	DCM[c]	
TM-01	3-NO_2	53	47	60.5	87.2	202.6-204.6
TM-02	3,4-diCl	28	47	76.9	45.7	193.2-195.2
TM-03	4-F	52	40	74.6	63.4	167.1-169.0
TM-04	4-Cl	41	45	53.1	68.0	196.4-198.2
TM-05	3-Br	47	40	54.2	41.2	204.8-205.6
TM-06	4-Br	47	40	47.6	34.3	221.7-223.5
TM-07	H	33	36	43.4	66.2	163.5-164.8
TM-08	4-CH_3	64	25	41.4	45.8	165.3-167.5
TM-09	3,4-diCH_3	64	26	44.1	35.5	152.9-154.5
TM-10	4-*i*-Bu	75	25	30.5	39.7	127.1-128.9
TM-11	4-OCH_3	67	18	28.1	18.3	210.5-212.8
TM-12	3-OAc (R^1)	25	/	70.0	/	151.1-152.5
TM-13	4-OAc (R^1)	20	/	60.5	/	157.8-159.2
TM-14	3-OH	5		56.2		160.1-161.5
TM-15	4-OH	1		65.5		243.0-244.8

[a] The reactions were performed in the following amount: *p*-nitrophenylacetonitrile (1.0 mmol), *m*-chlorobenzaldehyde (1.2 mmol), and aryl methyl ketones (1.2 mmol).

[b] at 45

[c] at 35

Scheme 1. The improved Dakin-West reaction among *p*-nitrophenylacetonitrile, *m*-chlorobenzaldehyde and aryl alkyl ketones



R=3-NO_2, 3, 4-diCl, 4-F, 4-Cl, 3-Br, 4-Br, H, 4-CH_3, 4-*i*-Bu, 3, 4-diCH_3, 4-OCH_3, 4-OH, 3-OH; R^1=4-OAc, 3-OAc

Scheme 2. Plausible reaction pathway

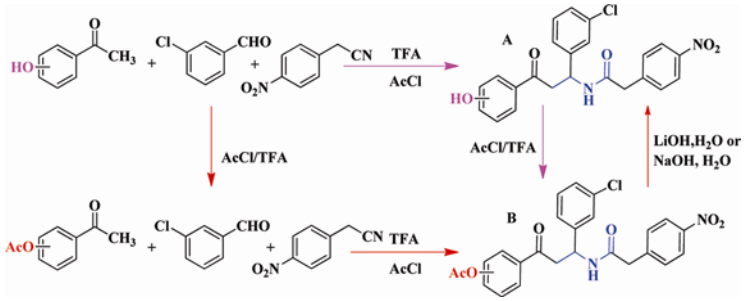


Figure 1. Time-yield-substituent relationships of $CHCl_3$ series

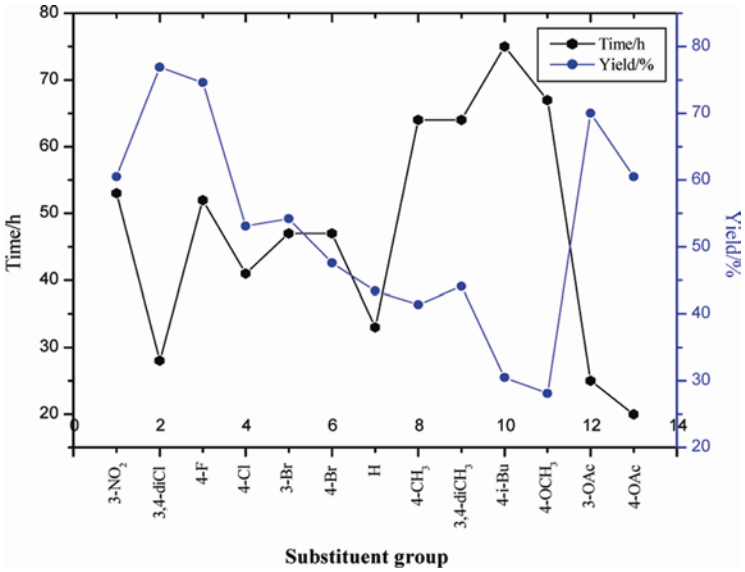


Figure 2. Time-yield-substituent relationships of DCM series

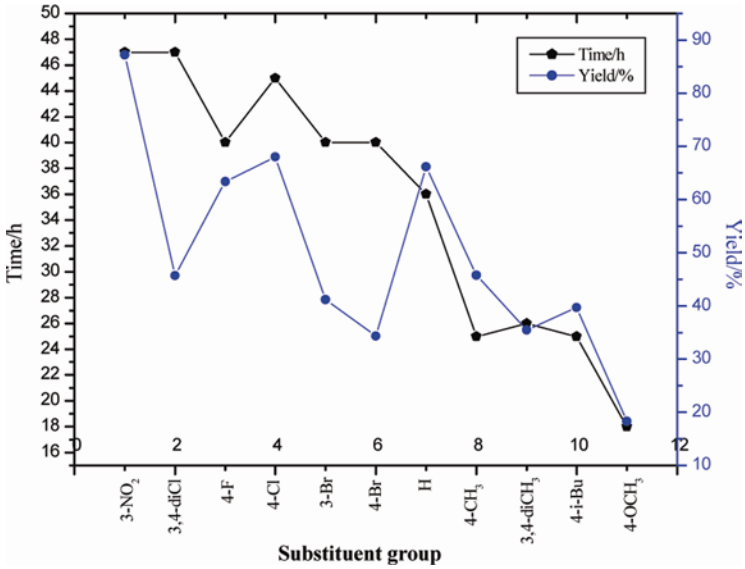


Figure 3. Suggested mechanism for the synthesis of *β*-arylacetamido ketone