Tetrahedron 72 (2016) 4889–4894

Contents lists available at ScienceDirect

Tetrahedron

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

AIBN-promoted amidation of anilines with 1, 3-diketones via oxidative cleavage of C–C bond under aerobic conditions

Sadu Nageswara Rao, Darapaneni Chandra Mohan, Subbarayappa Adimurthy *

Academy of Scientific & Innovative Research, CSIR-Central Salt & Marine Chemicals Research Institute, G. B. Marg, Bhavnagar, 364 002, Gujarat, India

ARTICLE INFO

Article history:
Received 26 May 2016
Received in revised form 22 June 2016
Accepted 23 June 2016
Available online 27 June 2016

Keywords:
Acylation
Anilines
1,3-Diketones
Amide synthesis
Selective cleavage

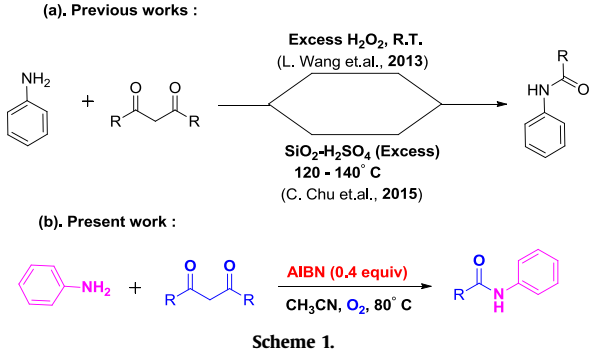
ABSTRACT

N-Acylation of anilines with 1, 3-diketones promoted by AIBN (2-2′-azoisobutyronitrile) under metal-free and peroxide-free conditions in the presence of molecular oxygen as oxidant has been described. This protocol proceeds by the oxidative cleavage of C–C bond with simultaneous intermolecular C–N bond formation under mild conditions.

1. Introduction

Functional group interconversion is one of the most important processes in organic synthesis. The selective transformation of amines into their corresponding amides is a crucial example among such interconversions due to the widespread use of amides in biology and in chemical synthesis. In addition, amides serve as versatile intermediates in the preparation of pharmaceuticals, agrochemicals and polymers.[1] Based on growing and important concept of amide synthesis in organic chemistry, many methods have been developed for their synthesis. Conventional amides are being synthesized by the reaction of amines with carboxylic acid derivatives with coupling reagents.[2] In the absence of a coupling reagent, the carboxylic acid derivatives and the amine simply form a carboxylate-ammonium salt, rather than an amide bond. According to a recently analyzed data set by medicinal chemistry campaigns, N-acylation of amines with activated carboxylic acids is the most common reaction performed in the synthesis of modern pharmaceuticals to construct the amide bond.[3] Several metal catalysts and oxidants have been identified for this process,[4,5] with the most promising catalysts being palladium[6] and copper/silver.[7]

In spite of these significant improvements, the development of novel and newer methods to construct amide bonds avoiding the need for multiple reaction steps, activating reagents, acidic or basic media and metal catalysts is an important goal in modern organic synthesis and deserves investigation. Nevertheless, the direct N-acylation through the C–C bond cleavage of ketones is still limited and attracts the continuous attention of chemists. In particular N-acylation by C–C bond cleavage of methyl ketones without metal is of prime importance, due to the fact that, the separation of metal catalyst from products for the synthesis of pharmaceuticals because their residual toxicity in the target compound is a central issue to consider. Wang and Chu developed N-acylation of aromatic amines through C–C bond cleavage to realize the transformations of ketones to amides under metal-free conditions (Scheme 1). Despite the significance of these novel reactions, the direct transformation of methyl ketones through C–C bond cleavage is still a fascinating theme.



Scheme 1.

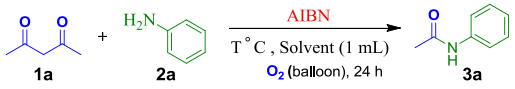
* Corresponding author. E-mail address: adimurthy@csmcri.org (S. Adimurthy).

http://dx.doi.org/10.1016/j.tet.2016.06.060
0040-4020/

2. Results and discussion

In the course of our research on *N*-alkylation and transamidation processes under metal-free conditions,[8] we initially aimed to realize the *N*-acylation of amines with 1,3-dicarbonyl compounds. With the hypothesis that, this transformation may occur by the radical initiator with molecular oxygen to cleave C–C bonds without peroxides we initiated the reaction. To our surprise, we observed the N-acylation of aniline with 1,3-dicarbonyl compound when 2-2′-azoisobutyronitrile (AIBN) was used as radical initiator (Scheme 1). In considering possible *N*-acylation partners by C–C bond cleavage with radical initiator, we elected to pursue the use of other radical initiators. To the best of knowledge, *N*-acylation of aniline by oxidative cleavage of the C–C bond without metal and oxidant have been scarcely investigated. Thus, we examined the *N*-acylation of aniline **2a** with 2, 4-pentanedione **1a** using 5 mol% of AIBN as radical initiator at 80 °C in acetonitrile under oxygen atmosphere, the desired product **3a** was isolated in 15% yield (Table 1, entry 1). The yield was improved by increasing the catalyst loading from 5 to 40 mol% (Table 1, entries 2–5). The reaction with 0.5 equiv of AIBN, yield of the desired product was suddenly dropped to 74% (Table 1, entry 6). It is notable that, O_2 is crucial for this *N*-acylation. Conducting the reaction in argon atmosphere shut down the reaction (Table 1, entry 7). The yield was dropped by lowering the reaction temperature (60 °C) and time (Table 1, entries 8 and 9). The reaction in other solvent systems like toluene, nitromethane and dichloroethane moderate yield (48–68%) of the *N*-acylated product was isolated (Table 1, entries 10–12). Moreover, other solvents were also examined (benzene, DMSO, DMF and DMA) failed to produce the desired product (Table 1, entries 13–16). Therefore, the optimization studies showed that 0.4 equiv of AIBN, at 80 °C in acetonitrile was found to be the best choice of conditions for this transformation.

Table 1
Optimization of reaction conditions for **3a**[a]

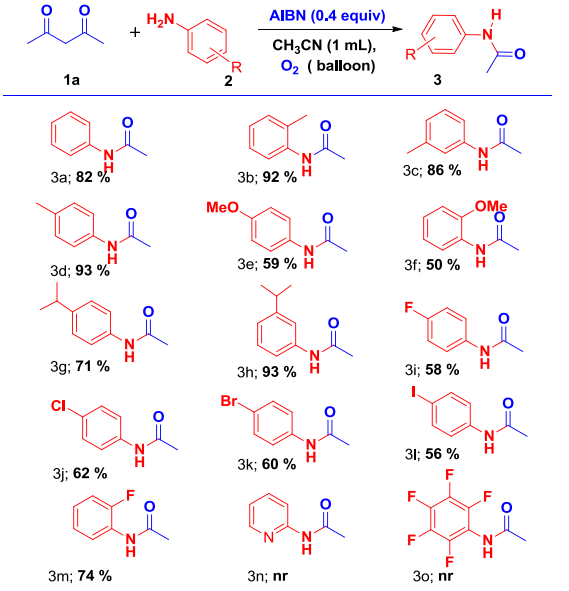


S.no.	AIBN (equiv)	Solvent (mL)	Temperature (°C)	Yield (%)
1	0.05	CH_3CN	80	15
2	0.1	CH_3CN	80	39
3	0.2	CH_3CN	80	41
4	0.3	CH_3CN	80	62
5	**0.4**	**CH_3CN**	**80**	**82**
6	0.5	CH_3CN	80	74
7[b]	0.4	CH_3CN	80	Trace
8	0.4	CH_3CN	60	46
9[c]	0.4	CH_3CN	80	62
10	0.4	Toluene	80	48
11	0.4	CH_3NO_2	80	58
12	0.4	DCE	80	68
13	0.4	Benzene	80	nr
14	0.4	DMSO	80	nr
15	0.4	DMF	80	nr
16	0.4	DMA	80	nr

Bold indicates the optimized conditions.
[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), AIBN (0.4 equiv), isolated yields.
[b] Reaction performed under argon atmosphere.
[c] Reaction carried out for 12 h.

Under these optimized conditions, the scope for N-acylation of various anilines were investigated using **1a** as *N*-acylating agent (Table 2). The presence of electron donating substituents (Me, OMe and ^{i}Pr) on anilines at *ortho*/*meta*/*para* positions reacted very smoothly and gave the desired *N*-acylated products **3b**–**3h** in good to excellent yields (50–93%). Furthermore, various anilines bearing electron withdrawing substituents on the benzene ring (F, Cl, Br, I) also gave the corresponding *N*-acylated products **3i**–**3m** in moderate to good yields. Under the optimized conditions, no desired product formation was observed with 2-aminopyridine and pentafluoro aniline. However, no reaction was observed with strong electron withdrawing groups present at the *meta* position of anilines. To expand the scope of the methodology, a variety of 1,3-diketones as source of acylating agents with various anilines were subjected to synthesize the functionalized amides (Table 3).

Table 2
Substrate scope for N-acylation of anilines with **1a**[a]



[a]Reaction conditions: **1a** (0.75 mmol), **2** (0.25 mmol), AIBN (0.4 equiv), CH_3CN (1mL), 80°C, for 24 h, Under Oxygen atmosphere.
[b] Isolated yields.

The reaction of 1-phenylbutane 1, 3-dione (**1b**) with 3-chloroaniline, 4-aminoacetophenone and 3,4-dimethoxy aniline under the optimized conditions gave the corresponding *N*-acylated products **4a**–**4c** in moderate to good yields. Similarly, the reaction of different 1, 3-diketones **1c**–**1f** were reacted with variety of substituted anilines and produced the desired amides **4d**–**4j** in good yields (56–76%). It may be noted that, in the case of unsymmetrical 1,3-diketones **1b**, and **1f**, the selective *N*-acylated products were observed rather than *N*-benzoylated and *N*-trifluoro acetylated products. These reactions clearly indicate that, this catalytic system is selective for the cleavage of aliphatic 1,3-diketones than aromatic ketones. However, the present methodology is not suitable for N-acylation of secondary amines and benzylic amines, which are not included in the table.

To assess the scope of the present methodology, we explored the N-acylation of variety of anilines with β-ketoesters instead of 1,3-diketones (Table 4). The reaction of β-ketoester **6a** with 4-(*sec*-butyl)aniline and 4-(*tert*-butyl)aniline gave the corresponding *N*-acylated products **4i** and **7a** in good yields (81% and 76%). Other β-ketoesters **6b** and **6c** with representative anilines gave corresponding *N*-acylated products in moderate to good yields. With β-ketoesters **6d** and **6e** no reaction was observed. Products from Tables 2–4 indicate the generality of the method with broad substrate scope.