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PII: S0040-4020(16)30582-8

DOI: 10.1016/j.tet.2016.06.060

Reference: TET 27874

To appear in: *Tetrahedron*

Received Date: 26 May 2016

Revised Date: 22 June 2016

Accepted Date: 23 June 2016

Please cite this article as: Rao SN, Mohan DC, Adimurthy S, AIBN−Promoted amidation of anilines with 1, 3-diketones via oxidative cleavage of C–C bond under aerobic conditions, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.06.060.

# AIBN–Promoted Amidation of Anilines with 1, 3-diketones via Oxidative Cleavage of C−C Bond under Aerobic Conditions

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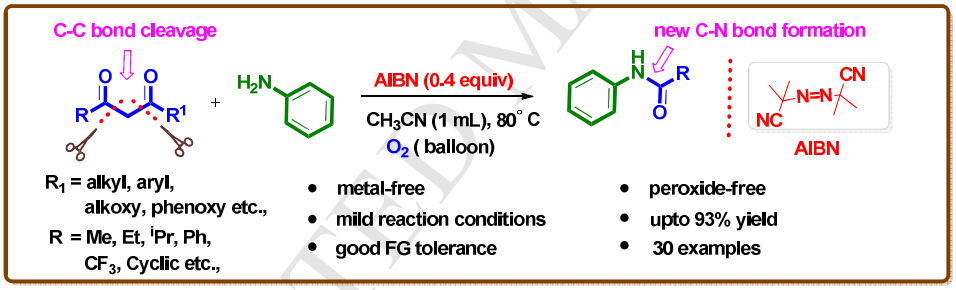
## Abstract:

*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.




**Keywords**: Acylation, Anilines, 1,3-diketones, amide synthesis, selective cleavage

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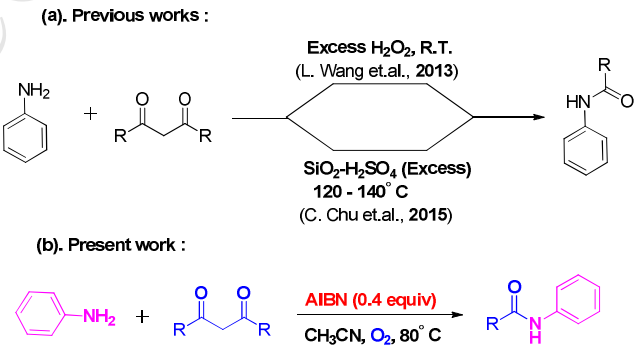
## 1. Introduction

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, 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



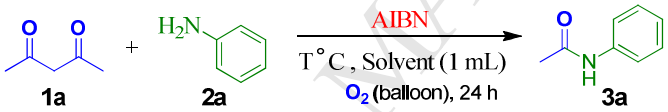

**Scheme 1.**

novel reactions, the direct transformation of methyl ketones through C−C bond cleavage is still a fascinating theme.

## 2. Results and Discussion

In the course of our research on *N*−alkylation and transamidation processes under metal-free conditions, 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

**Table1.** Optimization of reaction conditions for **3a**[a]




**1a** **2a** **3a**

| 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 |

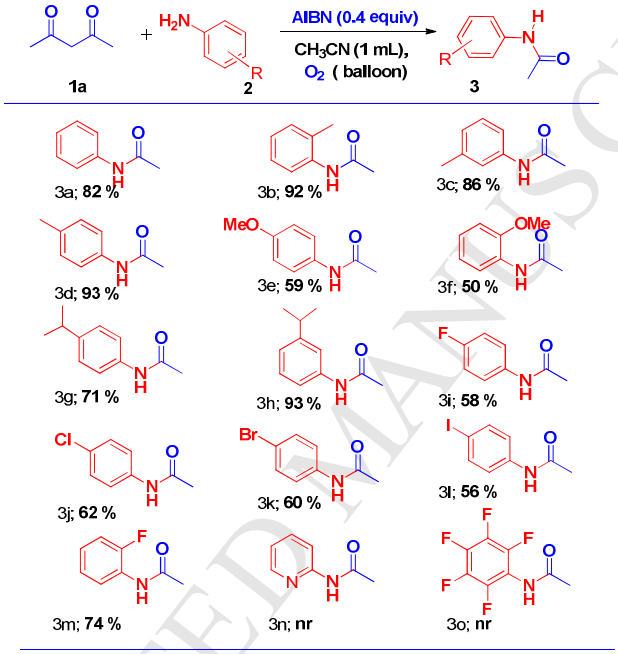
[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), AIBN (0.4 equiv), isolated yields. [b]Reaction performed under argon atmosphere. [c]Reaction carried out for 12 h.

*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 equivalent of AIBN, at 80°C in acetonitrile was found to be the best choice of conditions for this transformation.

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]

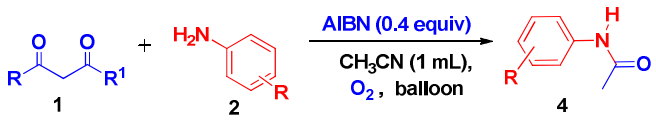



[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), AIBN (0.4 equiv), $CH_3CN$ (1mL), 80°C, for 24 h, Under Oxygen atmosphere. [b] Isolated yields.

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.

**Table3.** Scope of different β-diketones and anilines[a]

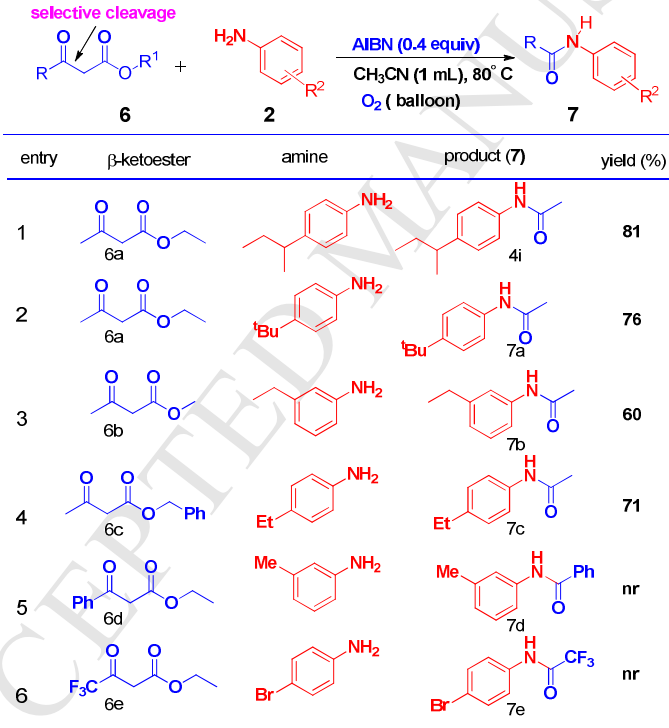



| entry | 1,3- diketone | aniline | product | yield (%) |
|---|---|---|---|---|
| 1. | 1b | | 4a | 65 |
| 2. | 1b | | 4b | 61 |
| 3. | 1b | | 4c | 48 |
| 4. | 1c | | 4d | 56 |
| 5. | 1c | | 4e | 69 |
| 6. | 1c | | 4f | 47 |
| 7. | 1d | | 4g | 56 |
| 8. | 1e | | 4h | 67<br>50[b] |
| 9. | 1f | | 4i | 58 |
| 10 | 1f | | 3h | 86 |
| 11 | 1g | | 4j | trace |

[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), 80°C, for 24 h, isolated yields. [b]Yield obtained with 1,3-diketone **1f.**

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 indicates the generality of the method with broad substrate scope.

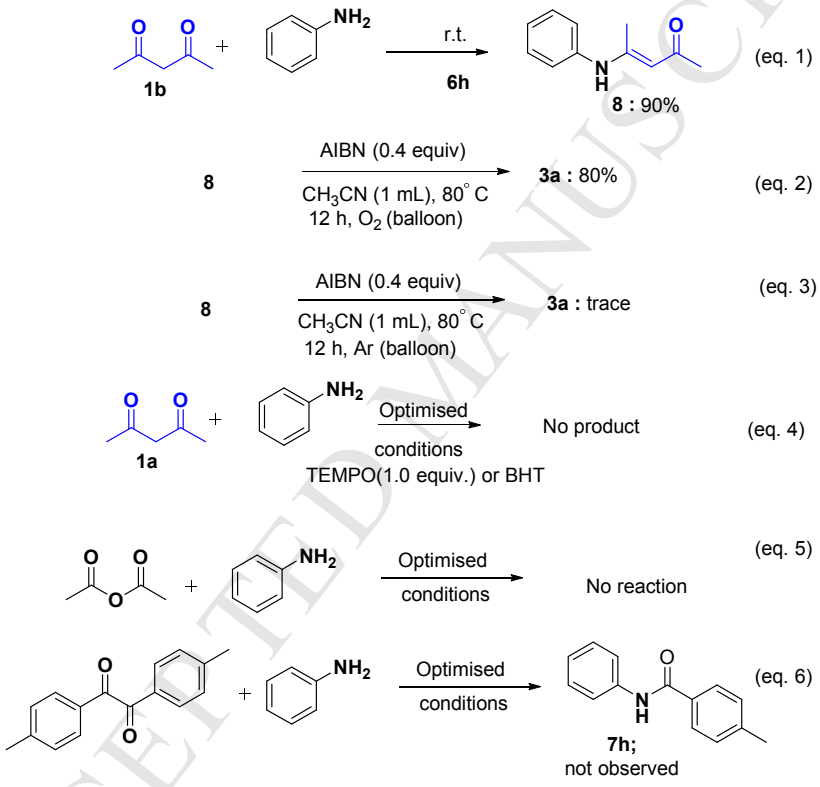
**Table4.** Scope of different β-ketoesters with anilines[a]




[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), isolated yields. nr = no reaction.

To gain insight into the reaction mechanism, some controlled experiments were carried out (Scheme 2). Initially, the reaction of 1,3-diketone **1a** was subjected with aniline at room temperature in open air under neat conditions, the enamine product **8** was isolated in 90% yield (Scheme 2, eq.1). When the enamine **8** was subjected to the optimized conditions, it afforded the

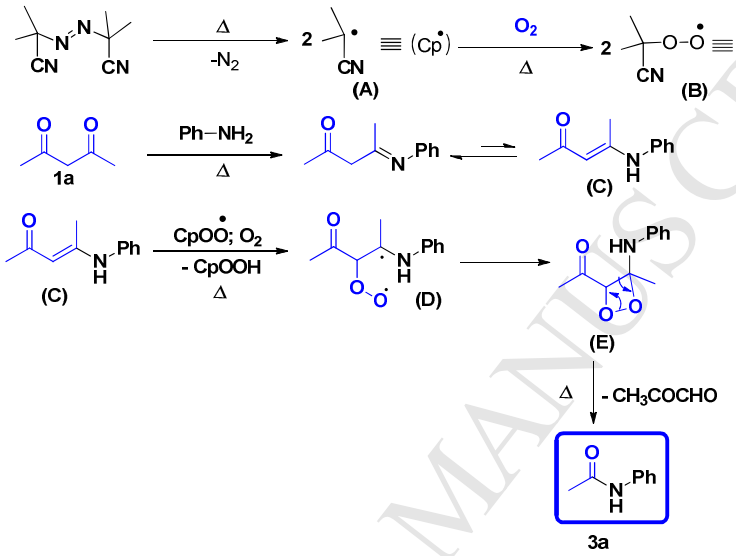
*N*-acylated product **3a** in 80% yield Scheme 2, eq.2). This reaction indicates that, the present system proceed through the enamine intermediate formation by reaction of 1,3-diketones and anilines which further undergoes hydrolysis to yield the desired product. Further we examined the reaction of enamine **8** with aniline under argon atmosphere instead of oxygen, only traces of desired product was observed (Scheme 1, eq.3). This reaction indicate the role of oxygen for the present transformation. To check the reaction pathway, **1a** and aniline was performed under




**Scheme 2.** Control experiments

optimized conditions with radical scavengers TEMPO and also with BHT, in both these cases no desired product formation was observed (Scheme 1, eq.4). Hence the present transformation proceed through radical mechanism. Under the optimized conditions, we subjected the reaction of aniline with acetic anhydride and 1,2-di-*p*-tolylethane-1,2-dione in place of 1,3-diketone to

check the acyl or benzoyl cleavage, however, the desired product was not observed (Scheme 1, eqs. 5 and 6). These reactions indicate the presence of methylene centre is essential between two keto groups. Also selective cleavage occurs at acyl position rather than benzoyl positions as indicated even in the discussion of Table 3 above.




**Scheme 3**. Plausible reaction mechanism.

Based on these above observations and literature reports, [8] the plausible reaction mechanism has been proposed (Scheme 3). Initially, AIBN under thermal conditions generate the radical species **A**, through the loss of nitrogen. Subsequently **A** in the presence of oxygen forms CPOO$^{\bullet}$ active radical species **B**. The condensation of 1,3-diketone 1a and aniline generates stable enamine intermediate **C** and its further reaction with **B**, generates peroxyradical intermediate **D**. Further cyclization of peroxyradical **D** form oxetane intermediate **E**. Finally thermal cleavage of **E** give the desired product **3a**.

## 3. Conclusions

In summary, we have developed a facile and operationally convenient method for the synthesis of amides via the oxidative cleavage of 1, 3-diketones with anilines promoted by AIBN, with molecular oxygen as terminal oxidant. The selective cleavage of acyl group was observed in the cases of unsymmetrical 1,3-diketones rather than benzoyl and trifluoro acyl groups. The present method not only eliminates the use of metals but also reduces the use of stoichiometric oxidants like peroxides for the synthesis of variety of amides with wide range of anilines and 1, 3-diketones in good to excellent yields.

**4. Experimental Section:**

**4.1. General:** All commercially available chemicals and reagents were used without any further purification unless otherwise indicated. $^{1}H$ and $^{13}C$ NMR spectra were recorded at 500, and 125 MHz, respectively. The spectra were recorded in $CDCl_3$ as solvent. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets), etc. and coupling constants (J) were given in Hz. Chemical shifts are reported in ppm relative to TMS as an internal standard. The peaks around delta values of $^{1}H$ NMR (7.2), and $^{13}C$ NMR (77.0) are correspond to deuterated solvent chloroform respectively. Mass spectra were obtained using electron impact (EI) ionization method. Progress of the reactions was monitored by thin layer chromatography (TLC). All products were purified through column chromatography using silica gel 100-200 mesh size using hexane/ethyl acetate as eluent unless otherwise indicated.

**4.2. General procedure for AIBN-Promoted Oxidative formation of Amides from Amines and 1, 3-Diketones (3a):** A sealed tube was equipped with a magnetic stir bar was charged with 1, 3-di-ketone **1a** (0.075 g, 0.75 mmol), aniline **2a** (0.0232 g, 0.25 mmol), AIBN (0.0164 g, 0.0001 mmol), and acetonitrile (1.0 mL). The above reaction mixture was stirred at 80 ºC under

$O_2$ atmosphere for 24 h. After completion of the reaction, the reaction was then cooled to room temperature, mixture was diluted with ethyl acetate. After removal of the solvent under reduced pressure the left out residue was purified by column chromatography using silica gel with hexane and ethyl acetate as eluent to get **3a** in 82 % yield (0.0278g). The spectral data was well matched with reported values. The above procedure is followed for the synthesis of all products reported in this manuscript.

**N-phenylacetamide (3a)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 82% yield (0.0278g); $^1$H NMR (500 MHz, CDCl3) $\delta$ 7.50(d, $J$ = 8.0 Hz, 2H), 7.32-7.26 (m, 3H), 7.11 (t, $J$ = 7.0 Hz, 1H), 2.17 (s, 3H) .$^{13}$C NMR (125 MHz, CDCl3) δ 168.4, 137.8, 128.9, 124.3, 119.9, 24.5.

**N-(o-tolyl)acetamide (3b)** [5b]

(Eluent: 25% EtOAc in Hexane); white solid; 92% yield (0.0343g); $^1$H NMR (500 MHz, CDCl3) $\delta$ 7.70 (d, $J$ = 8.5 Hz, 2H), 7.20-7.06 (m, 4H), 2.24(s, 2H), 2.17 (s, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.5, 135.6, 130.4, 129.6, 126.6, 125.4, 123.6, 29.7, 24.2, 17.7.

**N-(m-tolyl)acetamide (3c)** [5b]

(Eluent: 25% EtOAc in Hexane); white solid; 86% yield (0.0321g); $^1$H NMR (500 MHz, CDCl3) $\delta$ 7.34 (s, 1H), 7.26-7.17(m, 3H), 6.92(d, $J$ = 7.5 Hz, 1H), 2.33 (s, 3H), 2.16 (s, 3H) .$^{13}$C NMR (125 MHz, CDCl3) δ 168.3, 138.9, 137.7, 128.7, 125.1, 120.5, 116.9, 24.6, 21.4.

**N-(p-tolyl)acetamide(3d)** [5b]

(Eluent: 25% EtOAc in Hexane); white solid; 93% yield (0.0345g); $^1$H NMR (500 MHz, CDCl3) $\delta$ 7.46 (br s, 1H, NH), 7.37 (d, $J$ = 8.5 Hz, 2H), 7.10 (d , $J$ = 8.0 Hz, 2H), 2.30 (s, 3H), 2.13(s, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.5, 135.3, 133.9, 129.4, 120.1, 24.4, 20.8.

**N-(4-methoxyphenyl) acetamide (3e)** [5b]

(Eluent: 25% EtOAc in Hexane); white solid; 59% yield (0.0243g); $^{1}$H NMR (500 MHz, CDCl3) 7.61 (br s, 1H, NH ), $\delta$ 7.40 (d, $J$ = 9.0 Hz, 2H), 6.84 (d, $J$ = 9.0 Hz, 2H ), 3.77(s, 3H), 2.04(s, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.2, 156.2, 130.9, 121.7, 113.9, 55.2, 24.0.

**N-(2-methoxyphenyl)acetamide (3f)** [5c]

(Eluent: 25% EtOAc in Hexane); white solid; 50% yield (0.0208g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 8.36 (d, $J$ = 8.0 Hz, 1H), 7.76 (br s, 1H, NH ), 7.04 (t, $J$ = 7.5 Hz, 1H), 6.97 (t, $J$ = 7.5 Hz, 1H), 6.88 (d, $J$ = 8.5 Hz, 1H), 3.88 (s, 3H), 2.20 (s, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.1, 147.6, 127.7, 123.6, 121.1, 119.7, 109.8, 55.6, 24.9.

**N-(4-isopropylphenyl)acetamide (3g)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 71% yield (0.0337g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 7.68(br s, 1H, NH), 7.41(d, $J$ = 8.0 Hz, 2H), 7.15 (d, $J$ = 8.0 Hz, 2H), 2.88 (quin, $J$ =7.0 Hz 1H), 2.13(s, 3H), 1.22(d, $J$ = 7.0 Hz, 6H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.5, 144.9, 135.6, 126.8, 120.2, 33.5, 24.3., 24.0.

**N-(3-isopropylphenyl)acetamide (3h)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 93% yield (0.0422g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 7.48(t, $J$ = 7.5 Hz, 1H),7.41(br s, 1H, NH), 7.34 (s, 1H), 7.26-7.21(m, 1H), 6.98 (d, $J$ =7.5 Hz 1H), 2.90-2.86(m, 1H), 2.16(s, 3H), 1.23 (d, $J$ = 7.0 Hz, 6H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.3, 149.7, 137.7, 133.3, 129.9, 128.7, 128.2, 122.3, 117.9, 117.3, 33.9, 24.4, 23.7.

**N-(4-fluorophenyl)acetamide (3i)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 58% yield (0.0220g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 7.60 (br s, 1H, NH), 7.46-7.43 (m, 2H), 7.00 (t, $J$ = 8.5 Hz, 2H), 2.15 (s, 3H) .$^{13}$C NMR (125 MHz, CDCl3) δ 168.5, 160.3, 158.4, 133.8, 121.89, 121.83, 115.6, 115.4, 24.3.

**N-(4-chlorophenyl)acetamide (3j)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 62% yield (0.0261g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 7.45 (d, $J$ = 8.5 Hz, 2H), 7.32 (br s, 1H, NH), 7.28 (d, $J$ = 8.0 Hz, 2H), 2.17 (s, 3H) .$^{13}$C NMR (125 MHz, CDCl3) δ 168.3, 136.4, 128.9, 121.0, 24.5.

**N-(4-bromophenyl)acetamide (3k)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 60% yield (0.0323g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 7.44-7.36 (m, 5H), 2.16 (s, 3H). $^{13}$C NMR (125 MHz, CDCl3) δ 168.4, 136.9, 131.9, 121.3, 116.8, 24.5.

**N-(4-iodophenyl)acetamide (3l)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 56% yield (0.0364g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 7.59 (d, $J$ = 8.5 Hz, 2H), 7.35(br s, 1H, NH), 7.27(t, $J$ = 8.5 Hz, 2H), 2.14 (s, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.4, 137.9, 121.6, 87.4, 29.6, 24.6.

**N-(2-fluorophenyl)acetamide (3m)** [3l]

(Eluent: 30% EtOAc in Hexane); white solid; 74% yield (0.0283g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 8.30 (t, $J$ = 8.0 Hz, 1H), 7.42 (br s, 1H, NH ), 7.13-7.03 (m, 3H), 2.22 (s, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.4, 153.2, 151.3, 126.3, 126.2, 124.6, 124.38, 124.32, 121.8, 114.8, 114.6, 24.6.

**N-(3-chlorophenyl)acetamide (4a)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 65% yield (0.0276g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 7.81 (br s, 1H, NH ), 7.63 (s, 1H ), 7.35 (d, $J$ = 8.0 Hz, 1H), 7.22 (t, $J$ = 8.0 Hz, 1H), 7.07 (d, $J$ = 8.0 Hz, 1H), 2.17 (s, 3H), 1.29 (s, 9H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.7, 139.0, 134.5, 129.9, 124.3, 120.0, 117.8, 24.5.

**N-(4-acetylphenyl)acetamide (4b)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 61% yield (0.0271g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.96(br s, 1H, NH), 7.93 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 2.57 (s, 3H), 2.21(s, 3H), 1.22(d, *J* = 7.0 Hz, 6H).$^{13}$C NMR (125 MHz, CDCl3) δ 197.2, 168.8, 142.4, 129.7, 118.9, 26.4, 24.7.

**N-(3,4-dimethoxyphenyl)acetamide (4c)** [3n]

(Eluent: 30% EtOAc in Hexane); white solid; 48% yield (0.0254g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.36 (br s, 1H, NH), 7.30 (s, 1H), 6.87-6.85 (m, 1H), 6.79-6.78 (m, 1H), 3.85(d, *J* = 3.5 Hz, 6H), 2.15(s, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 163.2, 143.9, 140.7, 126.4, 106.9, 106.1, 100.0, 50.9, 50.7, 24.5, 19.3.

**N-phenylpropionamide (4d)** [5c]

(Eluent: 30% EtOAc in Hexane); white solid; 56% yield (0.0208g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.52 (d, *J* = 7.0 Hz, 2H), 7.35-7.29 (m, 3H`), 7.09 (br s, 1H, NH ),2.39 (d, *J* = 7.5 Hz, 2H), 1.25 (d, *J* = 7.0 Hz, 3H) .$^{13}$C NMR (125 MHz, CDCl3) δ 172.0, 137.9, 128.9, 124.1, 119.7, 30.7, 9.6.

**N-(p-tolyl)propionamide (4e)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 69% yield (0.0282g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.39 (d, *J* = 8.0 Hz, 2H), 7.33 (br s, 1H, NH ), 7.10 (d, *J* = 7.5 Hz, 2H), 2.38 (quar, *J* = 7.0 Hz, 2H) 2.30 (s, 3H), 1.24 (t, *J* = 7.5 Hz, 3H) .$^{13}$C NMR (125 MHz, CDCl3) δ 172.0, 135.4, 133.7, 129.4, 119.9, 30.6, 20.8, 9.7.

**N-(4-methoxyphenyl)propionamide (4f)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 47% yield (0.0212g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.41 (d, *J* = 9.0 Hz, 2H), 7.21 (br s, 1H, NH ), 6.85 (d, *J* = 8.5 Hz, 2H ), 3.78 (s, 3H), 2.38(quar, *J* = 7.5 Hz, 2H), 1.25 (d, *J* = 7.5 Hz, 3H) .$^{13}$C NMR (125 MHz, CDCl3) δ 171.7, 156.2, 130.9, 121.6, 113.9, 55.3, 30.4, 9.6.

**N-(3,4-dimethoxyphenyl)isobutyramide (4g)** [3o]

(Eluent: 30% EtOAc in Hexane); white solid; 56% yield (0.0314g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.26 (s, 1H), 7.11 (br s, 1H, NH ), 6.83-6.78 (m, 2H), 3.88 (s, 3H), 3.85 (s,3H), 2.52 (quin, *J* = 6.5 Hz, 1H), 1.26 (d, *J* = 6.5 Hz, 6H).$^{13}$C NMR (125 MHz, CDCl3) δ 175.0, 149.0, 145.6, 131.7, 111.37, 111.31, 104.8, 56.1, 55.8, 36.6, 19.6.

**N-(4-(trifluoromethyl)phenyl)acetamide (4h)** [5d]

(Eluent: 30% EtOAc in Hexane); white solid; 67% yield (0.0341g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.64 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 9.0 Hz, 2H ), 7.46 (br s, 1H, NH ), 2.21 (s, 3H), 1.25-1.20 (m, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.7, 140.9, 126.2, 122.9, 119.5, 119.3, 24.6.

**N-(4-(sec-butyl)phenyl)acetamide (4i)**

(Eluent: 30% EtOAc in Hexane); white solid; 58% yield (0.0275g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.40 (d, *J* = 8.0 Hz, 2H ), 7.24 (br s, 1H, NH), 7.13 (d, *J* = 8.0 Hz, 2H), 2.58 (q, *J* = 7.0 Hz, 1H), 2.15(s, 3H), 1.59 (quin, *J* = 7.5 Hz, 2H), 1.21 (d, *J* = 7.0 Hz, 2H), 0.81 (t, *J* = 7.5 Hz, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.2, 143.8, 135.5, 127.5, 120.0, 41.1, 31.1, 24.5, 21.8, 12.1. HRMS calcd for $C_{12}H_{18}NO$: 192.1388. Found: 192.1392.

**N-(4-(tert-butyl)phenyl)acetamide (7a)** [3n]

(Eluent: 30% EtOAc in Hexane); white solid; 76% yield (0.0362g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.41 (d, *J* = 7.5 Hz, 3H), 7.33 (d, *J* = 8.5 Hz, 2H ), 2.14 (s, 3H), 1.29 (s, 9H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.3, 147.2, 135.2, 125.7, 119.8, 34.3, 31.3, 24.4.

**N-(3-ethylphenyl)acetamide (7b)** [3m]

(Eluent: 30% EtOAc in Hexane); white solid; 60% yield (0.0244g); $^{1}$H NMR (500 MHz, CDCl3) *δ* 7.41(br s, 1H, NH), 7.35-7.29 (m, 2H), 7.26-7.19 (m, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 2.64 (quar, *J* = 7.5 Hz, 2H), 2.15(s, 3H), 1.25-1.20 (m, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 168.4, 145.2, 137.8, 128.8, 123.9, 119.4, 117.2, 28.8, 24.5, 15.4.

**N-(4-methoxyphenyl)propionamide (7c)** [5b]

(Eluent: 30% EtOAc in Hexane); white solid; 71% yield (0.0288g); $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 7.40 (d, $J$ = 8.0 Hz, 1H), 7.36 (br s, 1H, NH ), 7.14 (d, $J$ = 8.0 Hz, 2H ), 4.14(quar, $J$ = 7.5 Hz, 1H), 2.62(quar, $J$ = 7.5 Hz, 2H), 2.15 (s, 2H), 2.04 (s, 1H), 1.27 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl3) δ 168.1, 140.2, 135.3, 128.6, 128.5, 128.1, 120.2, 119.9, 28.1, 24.3, 15.4.

**(E)-4-(phenylamino)pent-3-en-2-one (8)** [5b]

(Eluent: 30% EtOAc in Hexane); yellow solid; 90% yield: $^{1}$H NMR (500 MHz, CDCl3) $\delta$ 12.4 (br s, 1H, NH ), 7.35 (t, $J$ = 7.5 Hz, 2H), 7.20 (t, $J$ = 7.5 Hz, 1H ), 7.11 (d, $J$ = 8.0 Hz, 2H), 5.18(s, 1H), 2.09 (s, 3H), 1.99 (s, 3H).$^{13}$C NMR (125 MHz, CDCl3) δ 196.0, 160.0, 138.6, 128.9, 125.4, 124.6, 97.4, 29.0, 19.6.

**ACKNOWLEDGMENT**

CSIR-CSMCRI Communication No.66/2016. S.N.R is thankful to AcSIR for his Ph.D. enrollment and the “Analytical Discipline and Centralized Instrumental Facilities” for providing instrumentation facilities. S.N.R. is also thankful to CSIR, New Delhi for his fellowship. We thank DST, Government of India (SR/S1/OC-13/2011), and CSIR-CSMCRI (OLP-087) for financial support.

**Supplementary Data:** Supplementary data related to this article can be found at http://

dx.doi.org/10.1016/j.tet.2016.

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