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A modified procedure for the Dakin–West reaction: an efficient and convenient method for a one-pot synthesis of β-acetamido ketones using silica sulfuric acid as catalyst

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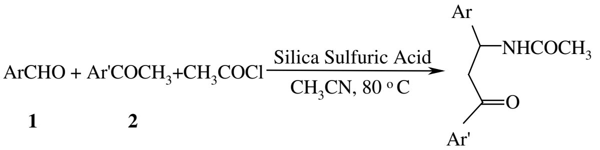
Abstract—A one-pot, four-component condensation of an aryl aldehyde, an aryl ketone, acetyl chloride and acetonitrile in the presence of silica sulfuric acid as an active, inexpensive, recoverable and recyclable catalyst is disclosed for the synthesis of β-acetamido ketones.

During the last few years, multi-component reactions (MCRs) have proved to be remarkably successful in generating molecular complexity in a single synthetic operation.[1] These processes consist of two or more synthetic steps, which are performed without isolation of any intermediates thus reducing time and saving both energy and raw materials. MCRs are powerful tools in the modern drug discovery process and allow fast, automated and high throughput generation of organic compounds.[2] Furthermore, a field of increasing interest is the synthesis of useful synthetic building blocks via MCR chemistry. For this reason, the discovery of novel MCRs is of interest.[3–5]

β-Acetamido ketones are versatile intermediates in that their skeletons exist in a number of biologically or pharmacologically important compounds.[6,7] The best known route for the synthesis of these compounds is the Dakin–West reaction,[8] which involves the condensation of an α-amino acid with acetic anhydride in the presence of a base via an intermediate azalactone to give the α-acetamido ketones.[9] Iqbal et al. proposed another procedure for the formation of these compounds through the condensation of an aryl aldehyde, acetophenone and acetyl chloride in acetonitrile in the presence of $CoCl_2$[10a] or montmorillonite K-10 clay.[10b] Although, this method is valuable, the time for the completion of this transformation is long (7 h). Therefore, the introduction of new and efficient methods for this multi-component reaction is still necessary. Towards this goal, and in continuation of our investigations on the synthesis of β-enaminones[11] and MCRs,[12] we were prompted to explore new methods for this useful transformation.

In recent years, heterogeneous catalysts have gained importance due to environmental and economic considerations.[13] Among these, the application of silica sulfuric acid as a stable and efficient heterogeneous catalyst in organic synthesis has been widely studied.[14] This catalyst is important from an environmental point of view, because it produces little waste. It also has excellent activity and selectivity even on an industrial scale and in most cases can be recovered from reaction mixtures and reused.

Now, we report an efficient and convenient procedure for the synthesis of β-acetamido ketones using silica sulfuric acid as catalyst (Scheme 1).



Scheme 1.

Keywords: β-Acetamido ketones; Benzaldehydes; Acetophenones; One-pot synthesis; Silica sulfuric acid; Catalyst; Dakin–West reaction.

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Table 1. One-pot condensation of aryl aldehydes, aryl ketones, acetyl chloride and acetonitrile to give the corresponding β-acetamido ketones catalyzed by silica sulfuric acid

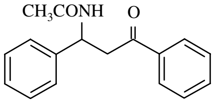
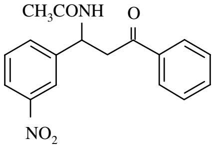
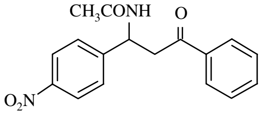
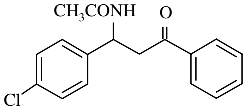
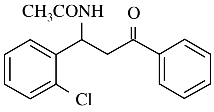
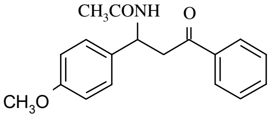
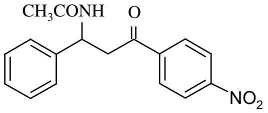
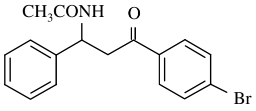
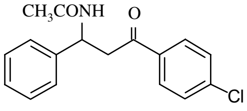
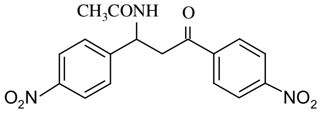
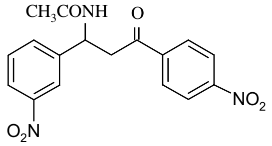
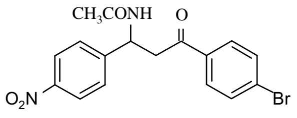
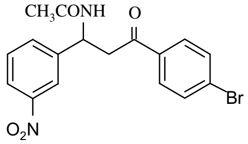
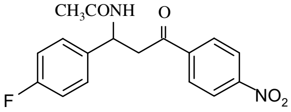
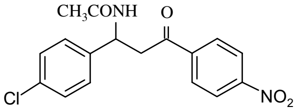
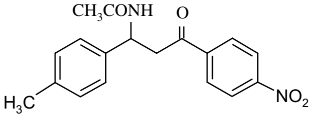
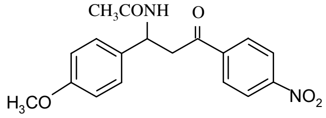
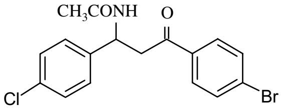
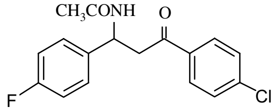
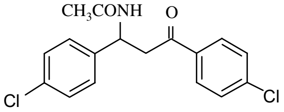
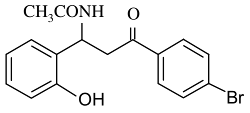
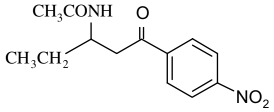
Entry	Ar	Ar′	Product[a]	Time (min)	Yield %[b]
1	C_6H_5	C_6H_5		65	91
2	$3\text{-}NO_2C_6H_4$	C_6H_5		120	80
3	$4\text{-}NO_2C_6H_4$	C_6H_5		110	82
4	$4\text{-}ClC_6H_4$	C_6H_5		70	89
5	$2\text{-}ClC_6H_4$	C_6H_5		95	93
6	$4\text{-}CH_3OC_6H_4$	C_6H_5		80	84
7	C_6H_5	$4\text{-}NO_2C_6H_4$		90	90
8	C_6H_5	$4\text{-}BrC_6H_4$		80	93
9	C_6H_5	$4\text{-}ClC_6H_4$		70	90
10	$4\text{-}NO_2C_6H_4$	$4\text{-}NO_2C_6H_4$		100	75
11	$3\text{-}NO_2C_6H_4$	$4\text{-}NO_2C_6H_4$		100	82
12	$4\text{-}NO_2C_6H_4$	$4\text{-}BrC_6H_4$		90	92

Table 1 (*continued*)

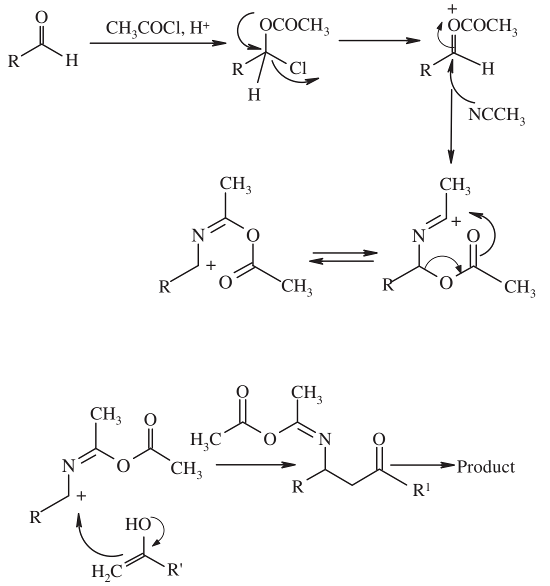
Entry	Ar	Ar′	Product[a]	Time (min)	Yield %[b]
13	3-$NO_2C_6H_4$	4-BrC_6H_4		90	89
14	4-FC_6H_4	4-$NO_2C_6H_4$		90	80
15	4-ClC_6H_4	4-$NO_2C_6H_4$		70	87
16	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$		100	70
17	4-$CH_3OC_6H_4$	4-$NO_2C_6H_4$		65	88
18	4-ClC_6H_4	4-BrC_6H_4		60	94
19	4-FC_6H_4	4-ClC_6H_4		100	87
20	4-ClC_6H_4	4-ClC_6H_4		65	91
21	2-HOC_6H_4	4-BrC_6H_4		70	72
22	CH_3CH_2	4-$NO_2C_6H_4$		120	30

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

[b] Isolated yields.

The experimental procedure for this reaction is remarkably simple and requires no inert atmosphere.[15] We started our investigation using aryl aldehydes and aryl ketones as substrates. The reaction was carried out by stirring an aryl aldehyde, an aryl methyl ketone and acetyl chloride with silica sulfuric acid in acetonitrile at 80 °C. The results obtained are summarized in Table 1. All the products were characterized by ^{1}H or ^{13}C NMRs spectroscopic data.

Aromatic aldehydes or acetophenones both with activating and deactivating groups underwent smooth



Scheme 2.

transformation to the corresponding β-acetamido ketones, without the formation of any side products, in high to excellent yields and in relatively short reaction times (<120 min). However, the synthesis could not be achieved in the absence of the catalyst.

Several functional groups such as nitro chloro, bromo, hydroxyl and methoxy were compatible with this procedure (Table 1, entries 2–21). Interestingly, we found that no acetylation of an aromatic hydroxyl group was observed under the reaction conditions and the corresponding β-acetamido ketone was isolated in an excellent yield (Table 1, entry 21). We found that aliphatic aldehydes react under these conditions, but produce the corresponding β-acetamido ketones in low yields (Table 1, entry 22). The catalyst can be easily prepared and can be handled safely. It can also be recovered and reused at least five times without losing activity.

We propose a reaction mechanism based on Iqbal's suggestion[10a] for the formation of β-acetamido ketones in Scheme 2. The presence of acetyl chloride is necessary for the transformation and the reaction in its absence gave none of the desired product even after 2 h.

In conclusion, we have developed a simple methodology for the one-pot synthesis of β-acetamido ketones by coupling four components, viz benzaldehydes, acetophenones, acetyl chloride and acetonitrile catalyzed by the reusable solid acid, silica sulfuric acid.

Acknowledgements

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15. The general procedure is as follows: a solution of the aryl aldehyde (1 mmol), aryl ketone (1 mmol), acetyl chloride (0.3 mL) and acetonitrile (2 mL) in the presence of silica sulfuric acid (0.3 g, equal to 0.78 mmol H^+) was heated at 80 °C, with stirring for 60–120 min. The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was filtered and the filtrate poured into 50 mL ice-water. The solid product was filtered, washed with ice-water and recrystallized from ethyl acetate/*n*-heptane to give the pure product. Most of the compounds prepared are known.[10b] The spectral data of some representative β-acetamido ketones are given below. β-Acetamido-β-(4-chlorophenyl)propiophenone (Table 1, entry 4): mp 146–148 °C, IR (NaCl, cm^{-1}) 3280, 3072, 1680, 1641, 1542, 1283, 1088, 892, 812, 690, ^1H NMR ($CDCl_3$, 200 MHz) δ 2.10 (s, 3H), 3.49 (dd, J = 7.8 and 10.9 Hz, 1H), 3.83 (dd, J = 7.8 and 10.9 Hz, 1H), 5.62 (m, 1H), 7.18 (m, 5H), 7.51 (m, 3H), 7.94 (d, J = 9.1 Hz, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.8, 43.4, 49.7, 128.4, 128.5, 129.1, 129.2, 133.5, 134.1, 136.8, 140.1, 170.0, 198.7. β-Acetamido-β-(4-chlorophenyl)-4-chloropropiophenone (Table 1, entry 20): mp 141–143 °C, IR (NaCl, cm^{-1}) 3264, 3056, 1670, 1635, 1584, 1292, 1088, 885, 825, ^1H NMR ($CDCl_3$, 200 MHz) δ 2.08 (s, 3H), 3.40 (dd, J = 7.3 and 10.9 Hz, 1H), 3.82 (dd, J = 7.3 and 10.9 Hz, 1H), 5.57 (m, 1H), 7.32 (s, 1H), 7.47 (d, J = 9.1 Hz, 4H), 7.90 (d, J = 9.1 Hz, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.5, 43.6, 49. 9, 128.4, 129.3, 129.5, 129.9, 133.8, 135.1, 139. 7, 140.6, 170.5, 197.3.