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Trifluoromethanesulfonic acid promoted Dakin–West reaction: An efficient and convenient synthesis of *β*-acetamido ketones

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Abstract. Trifluoromethanesulfonic acid promoted efficient condensation of an aromatic aldehyde with an acetophenone and acetonitrile in the presence of acetylchloride as an activator producing *β*-acetamido carbonyl compounds is described.

Keywords. *β*-Acetamido ketones; Dakin–West reaction; multicomponent synthesis; trifluoromethanesulfonic acid.

1. Introduction

β-Acetamido carbonyl compounds are valuable building blocks for the preparation of 1,3-amino alcohols[1,2] or *β*-amino acids,[3] as well as for the synthesis of various bioactive molecules such as the antibiotics nikkomycins and neopolyoxines.[4,5] The conventional way for the preparation of these compounds is by the Dankin–West[6] reaction using a *α*-amino acid and acetic anhydride. Later on, Iqbal *et al.* introduced another procedure for the formation of these compounds through the condensation of an acetophenone, an aryl aldehyde in acetonitrile in the presence of $CoCl_2$[7] or montmorillonite K-10 clay as a catalyst and acetyl chloride as a promoter.[8] Subsequently, this reaction was studied using acetyl chloride as a promoter in the presence of several other catalysts such as $Cu(OTf)_2/Sc(OTf)_3$,[9] BiOCl,[10] $ZrOCl_2.8H_2O$,[11] heteropoly acid,[12,13] I_2,[14] amberlyst-15,[15] ZnO,[16] and $CeCl_3$.[17] Although all these methods are useful, they suffer from limitations such as long reaction times and the handling and disposal of inorganic acids.

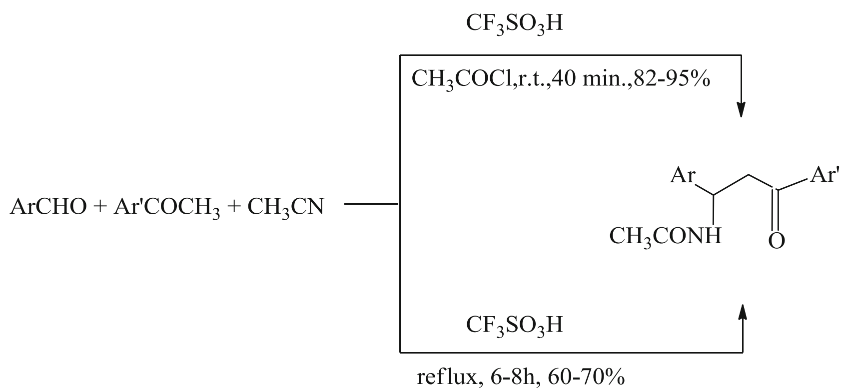
Trifluoromethanesulfonic acid or triflic acid is a well-known Bronsted super acid and it has been extensively studied as a catalyst in a wide range of organic transformations, which include cyclizations of unsaturated alcohols,[18] acylations of alcohols,[19] additions of allylboranes to aldehydes,[20] annelation of aromatic sulfonamides,[21] stereoselective Friedel–Crafts aminoalkylations of indoles and pyrroles[22] etc. Here, we report first observation of triflic acid promoted Dakin–West reaction of aromatic aldehydes, or acetophenones, with acetonitrile forming *β*-acetamido ketones in good yields (60–70%). However, when acetyl chloride was used in the reaction as an activator, we observed formation of *β*-acetamido carbonyl compounds with enhanced yield (82–95%) as shown in scheme 1. Representative results are given in table 1.

2. Experimental

2.1 *General procedure for the preparation of β-acetamido ketones with triflic acid and acetyl chloride*

To a stirred solution of 4-nitrobenzaldehyde (0.30 g, 2 mmol) and 4-nitroacetophenone (0.33 g, 2 mmol) in acetonitrile (5 mL) was added acetyl chloride (0.23 g, 3 mmol) and trifluoromethanesulfonic acid (0.2 mL, 2 mmol). The mixture was stirred at room temperature for 30 min. and the progress of reaction was monitored by TLC. After completion, the mixture was poured into crushed ice (10 g) and extracted with ethyl acetate (2×10 mL). The organic layer was washed successively with water (1×5 mL), saturated sodium bicarbonate solution (1×5 mL) and brine (1×5 mL), then dried over anhy. Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography to give *β*–acetamido–*β*-(4-nitrophenyl)-4-nitropropiophenone as a pale yellow solid (0.63 g, 88%, mp. 152°C). IR (KBr, cm^{-1}): 3280, 3072, 1690, 1646, 1590, 1530, 1358, 1073, 995, 816, 759. ^{1}H NMR

*For correspondence



Scheme 1. Trifluoromethanesulfonic acid promoted Dakin–West reaction.

Table 1. Trifluoromethanesulfonic acid catalysed synthesis of β-acetamido carbonyl compounds.

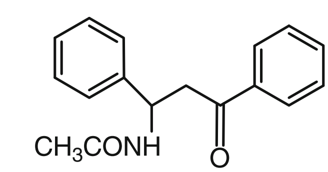
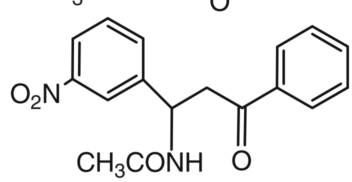
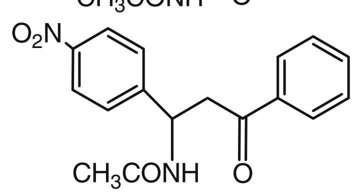
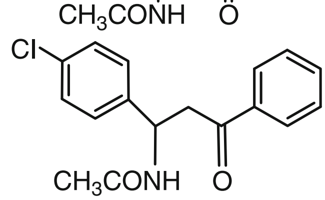
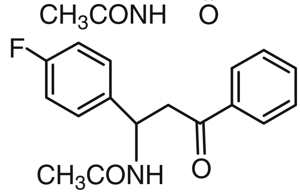
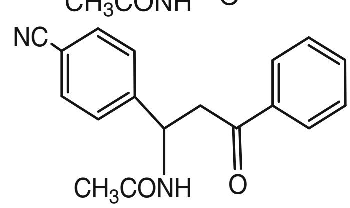
Entry	Ar	Ar'	Product[a]	Time Min(h)	mp °C	Yield[c] %
1	C_6H_5	C_6H_5		35 (8)[d]	104[b]	89 (60)[d]
2	$3\text{-}NO_2C_6H_4$	C_6H_5		40 (6)[d]	115	87 (63)[d]
3	$4\text{-}NO_2C_6H_4$	C_6H_5		30 (7)[d]	150[b]	89 (63)[d]
4	$4\text{-}ClC_6H_4$	C_6H_5		25 (8)[d]	149[b]	87 (62)[d]
5	$4\text{-}FC_6H_4$	C_6H_5		35 (6)[d]	120[b]	86 (65)[d]
6	$4\text{-}CNC_6H_4$	C_6H_5		30 (7)[d]	88[b]	83 (62)[d]

Table 1. (continued)

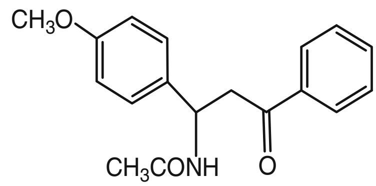
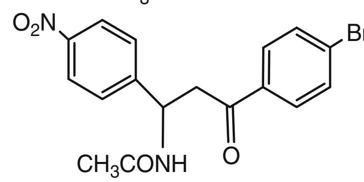
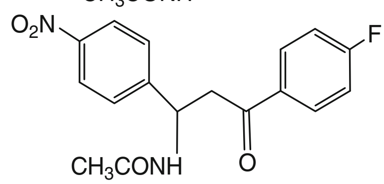
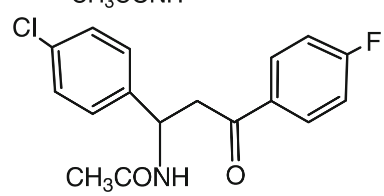
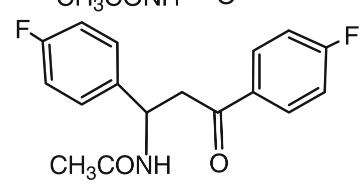
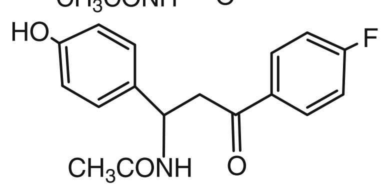
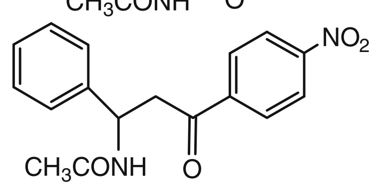
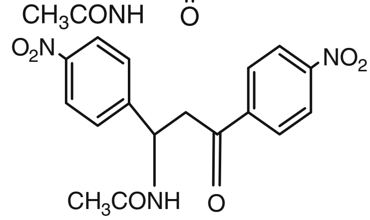
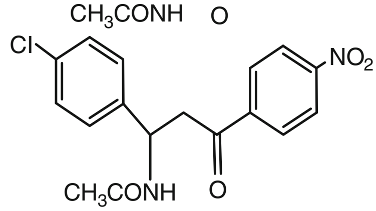
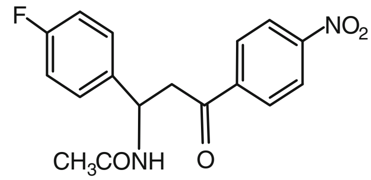
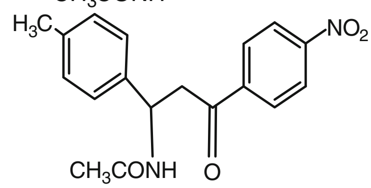
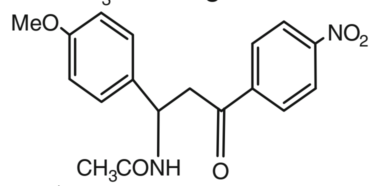
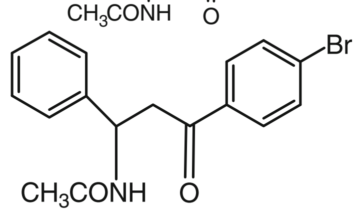
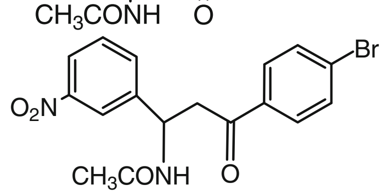
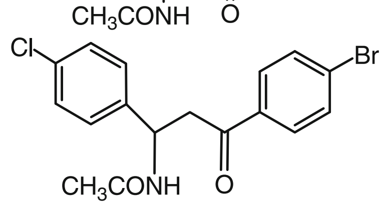
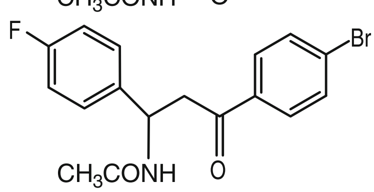
Entry	Ar	Ar'	Product[a]	Time Min(h)	mp °C	Yield[c] %
7	4-$MeOC_6H_4$	C_6H_5		25 (7)[d]	114[b]	91 (68)[d]
8	4-$NO_2C_6H_4$	4-BrC_6H_4		30	180[b]	91
9	4-$NO_2C_6H_4$	4-FC_6H_4		35 (8)[d]	147[b]	92 (68)[d]
10	3-ClC_6H_4	4-FC_6H_4		40	116[b]	89
11	4-FC_6H_4	4-FC_6H_4		30 (7)[d]	94[b]	91 (66)[d]
12	4-HOC_6H_4	4-FC_6H_4		35	132[b]	86
13	C_6H_5	4-$NO_2C_6H_4$		40 (8)[d]	75[b]	89 (64)[d]
14	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$		30 (8)[d]	152[b]	88 (62)[d]
15	4-ClC_6H_4	4-$NO_2C_6H_4$		30 (7)[d]	118	89 (60)[d]

Table 1. (continued)

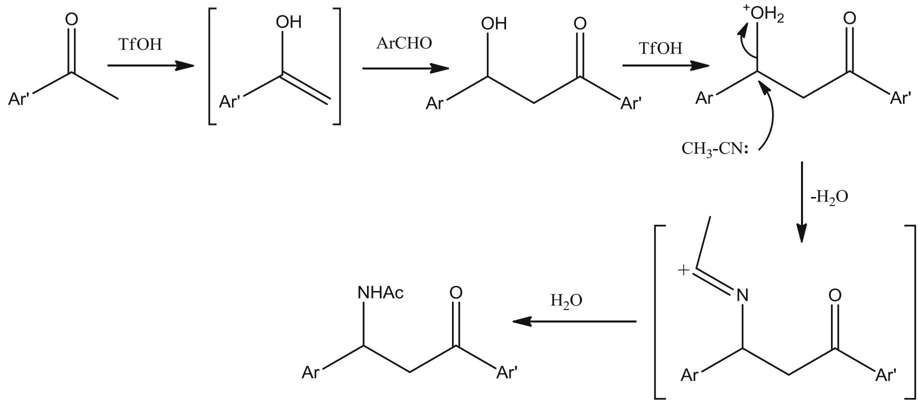
Entry	Ar	Ar'	Product[a]	Time Min(h)	mp °C	Yield[c] %
16	4-FC_6H_4	4-$NO_2C_6H_5$		35 (8)[d]	151[b]	95 (70)[d]
17	4-MeC_6H_4	4-$NO_2C_6H_4$		25	85[b]	82
18	4-$MeOC_6H_4$	4-$NO_2C_6H_4$		30 (7)[d]	88[b]	84 (68)[d]
19	C_6H_5	4-BrC_6H_4		40	99	86
20	3-$NO_2C_6H_4$	4-BrC_6H_4		40 (6)[d]	115[b]	87 (67)[d]
21	4-ClC_6H_4	4-BrC_6H_4		40 (7)[d]	141[b]	88 (63)[d]
22	4-FC_6H_4	4-BrC_6H_4		35 (7)[d]	221[b]	85 (60)[d]

[a]All products gave satisfactory IR, ^{1}H NMR, ^{13}C NMR and mass spectra. [b]These values were identical with the literature report.[7,8,10,23,24] [c]Isolated yields correspond to reaction with triflic acid and acetyl chloride. [d]Reaction times and yield given in parentheses correspond to the reaction with triflic acid.

(DMSO-D_6, 200 MHz): δ1.90 (s, 3H), 3.4 (dd, $J = 5.7$ and 13.8 Hz, 1H), 3.7 (dd, $J = 7.3$ and 13.8 Hz, 1H), 5.5 (dd, , $J = 7.3$ and 5.7 Hz, 1H), 7.62 (d, $J = 8.9$ Hz, 1H), 8.1–8.2 (m, 4H), 8.2–8.4 (m, 4H); ^{13}C NMR (DMSO-D_6, 50 MHz): δ 22.4, 44.3, 48.5, 123.1, 123.5, 127.7, 129.1, 140.7, 146.3, 149.8, 150.1, 169.1, 195.3; FABMS: 358($M^+ + 1$).

2.2 *General procedure for the preparation of β-acetamido ketones with triflic acid*

To a stirred solution of 4-anisaldehyde (0.27 g, 2 mmol) and acetophenone (0.24 g, 2 mmol) in acetonitrile (5 mL) were added triflic acid (0.2 mL, 2 mmol). The mixture was refluxed for 7 h and the progress of the



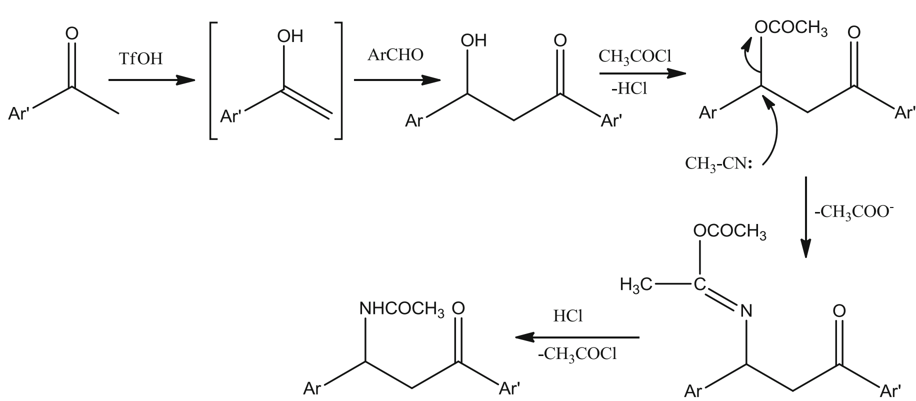
Scheme 2. Plausible mechanism for the triflic acid promoted Dakin–West reaction.

reaction was followed by TLC. After completion of the reaction, the mixture was poured into crushed ice (10 g) and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with water (1 × 5 ml), saturated sodium bicarbonate solution (1 × 5 mL) and brine (1 × 5 mL), dried over anhy. Na_2SO_4 and concentrated under vacuum. The crude product was purified by normal column chromatography to obtain β–acetamido–β-(4-methoxyphenyl) propiophenone as yellowish solid (0.40 g, 68%, mp 114°C). The isolated product gave the following spectral data: IR (KBr, cm^{-1}) 302, 3075, 2934, 1689, 1648, 1546, 1296, 1103, 887, 825.

^{1}HNMR (DMSO-D_6, 200 MHz): δ 2.0 (s, 3H), 3.3 (dd, $J = 6.8$ and 16.6 Hz, 1H), 3.7 (dd, $J = 5.3$ and 16.6 Hz, 1H), 5.5 (dd, $J = 5.3$ and 6.8 Hz, 1H), 6.8 (d, $J = 8.9$, 2H), 7.2 (d, $J = 8.9$, 2H), 7.4–7.5 (m, 3H), 7.9 (d, $J =$ 7.6 Hz, 2H); ^{13}C NMR (DMSO-D_6, 50 MHz): δ 22.2, 44.5, 49.0, 55.1, 101.0, 127.1, 128.2, 129.7, 133.1, 134.7, 136.3, 158.4, 169.1, 197.2. FABMS: 298 $(M+H)^+$.

3. Results and discussion

In most of the existing literature on Lewis acid catalysed Dakin–West reaction, acetyl chloride was widely used as an activator to promote the reaction. Later TMSCl[13] was also reported be a useful activator for promoting the Dakin–West reactions. In our study, we found efficient Dakin–West reactions with triflic acid alone without requiring acetyl chloride and obtained β-acetamido carbonyl compounds in 60–70% under reflux in acetonitrile. However, when this reaction was carried out using triflic acid as a catalyst and acetyl chloride as a promoter, reaction proceeded at room temperature producing β-acetamido carbonyl compounds with improved yields (82–95%). A plausible pathway for the formation of β-acetamido carbonyl compounds under both conditions, i.e., using triflic acid alone and also by using both triflic acid and acetyl chloride, are shown in schemes 2 and 3, respectively.



Scheme 3. Plausible mechanism for the triflic acid catalysed Dakin–West reaction in the presence of acetyl chloride as an activator.

4. Conclusion

In conclusion, the present work describes an efficient condensation of an aromatic aldehyde and acetophenones with acetonitrile using triflic acid as a promoter and acetyl chloride as an activator producing β-acetamido carbonyl compounds in good yields.

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