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Research Article

Facile Alkylation on Active Methylene Site of Carbonyl Compounds with Benzylic Alcohols

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ABSTRACT:

Triflic acid has found to be notable catalyst for the alkylation on active methylene sites of the 1,3-dicarbonyl compounds provides the alkylated compounds in excellent yields. Various monoalkylated products are provided on active methylene sites with different benzylic alcohols using the catalyst Triflic acid.

Keywords: 1, 3-dicarbonyl compounds, Triflic acid, C-C bond formation, Active methylene site and Mono alkylation.

[I] INTRODUCTION:

The formation of carbon–carbon single bonds is of fundamental importance in organic synthesis, which leads to synthesis of organic compounds that exhibit significant biological, pharmaceutical and material properties.

As a result, there are an ever-growing number of methods available for carbon–carbon bond formation. The alkylation on active methylene site of 1, 3-dicarbonyl compounds exhibits one of the most purposive methodologies for C-C bond forming reactions [1-3].

It is well known that carbonyl groups increase the acidity of the proton(s) adjacent to the carbonyl group. The acidity of the C-H bonds in these compounds is caused by a combination of the inductive electron-withdrawing effect of the unsaturated groups and the resonance stabilization of the anion formed by removal of a proton.

Not all groups are equally effective in 'activating' a neighbouring CH; nitro is the most powerful of the common groups, with the series following the approximate order NO_2>COR>SO_2R>CO_2R>CN>C_6H_5. Two activating groups reinforce each other; for example, diethyl malonate has a lower pKa(≈13) than ethyl acetate (pKa≈24).

Acidity is increased slightly by electronegative substituents. Removal of a proton from the alpha-carbon atom of a carbonyl compound with base gives the corresponding enolate anion. It is these enolate anions that are involved in many reactions of carbonyl compounds, such as the aldol condensation, and in bimolecular nucleophilic displacements. Enolate anions should be distinguished from enols, which are always present in equilibrium with the carbonyl compound. Most monoketones and esters

contain only small amounts of enol (<1%) at equilibrium, but with 1,2- and 1,3-dicarbonyl compounds much higher amounts of enol (>50%) may be present. In the presence of a protic acid, ketones may be converted largely into the enol form, implicated in many acid-catalysed reactions of carbonyl compounds. The presence of hexamethylphosphoramide (HMPA) or a triamine or tetramine can also enhance the rate of alkylation. This is thought to be because of the fact that these solvents or additives solvate the cation, but not the enolate, thereby separating the cation–enolate ion pair [4]. This leaves a relatively free enolate ion, which would be expected to be a more reactive [5] nucleophile than the ion pair.

A difficulty sometimes encountered in the alkylation of active methylene compounds is the formation of unwanted dialkylated products. During the alkylation of the sodium salt of diethylmalonate, the monoalkyl derivative formed initially is in equilibrium with its anion. In ethanol solution, dialkylation does not take place to any appreciable extent because ethanol is sufficiently acidic to reduce the concentration of the anion of the alkyl derivative, but not that of the more acidic diethylmalonate itself, to a very low value. However, replacement of ethanol by an inert solvent favours dialkylation. Dialkylation also becomes a more serious problem with the more acidic cyanoacetic esters and in alkylations with very reactive electrophiles such as allyl or benzyl halides or sulfonates.

Under ordinary conditions, aryl or alkenyl halides do not react with enolate anions, although reaction can occur with aryl halides bearing strongly electronegative substituents in the ortho and para positions. An undesired side reaction which sometimes occurs in the alkylation of 1,3-dicarbonyl compounds is the formation of the O-alkylated product.

In general, however, O-alkylation competes significantly with C-alkylation only with reactive methylene compounds in which the equilibrium concentration of enol is relatively high (as in 1,3-dicarbonyl compounds). The extent of C- versus O-alkylation for a particular 1,3-dicarbonyl compound depends on the choice of cation, solvent and electrophile. Cations (such as Li^+) that are more covalently bound to the enolate oxygen atom [6] or soft electrophiles (such as alkyl halides) favour C-alkylation, whereas cations such as K^+ or hard electrophiles (such as alkyl sulfonates) favour O -alkylation.

Alkylation of symmetrical ketones or of ketones that can enolize in one direction only can, of course, give just one mono-C-alkylated product. With unsymmetrical ketones, however, two different monoalkylated products may be formed by way of the two structurally isomeric enolate anions [7]. If one of the isomeric enolate anions is stabilized by conjugation with another group, such as cyano, nitro or a carbonyl group, then only this stabilized anion is formed and alkylation takes place at the position activated by both groups. Even a phenyl or an alkenyl group provide sufficient stabilization of the resulting anion to direct substitution into the adjacent position [8-9].

[II]. MATERIALS AND METHODS:

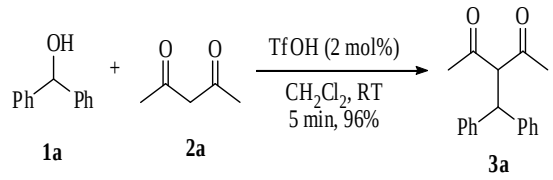
^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on 300 MHz, 500 MHz or 75 MHz spectrometer at ambient temperature. Chemical shifts δ is given in ppm, coupling constant J are in Hz. The chemical shifts are reported in ppm on scale downfield from TMS as internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; td, triplet of doublet; t, triplet; m, multiplet; br s, broad singlet. FTIR spectra were recorded as KBr thin films or neat. For low (MS) and High (HRMS) resolution, *m/z* ratios are reported as values in atomic mass units. All the reagents and solvents were reagent grade and used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to

use. Column chromatography was carried out using silica gel (60-120 mesh) packed in glass columns.

[III]. EXPERIMENTAL:

Explored the utility of Triflic acid as a catalyst for the alkylation of 1, 3-dicarbonyl compounds using alcohols as the alkylating agents. Triflic acid is commercially available reagent. Nevertheless, we have successfully demonstrated the utility of Triflic acid in the alkylation of 1,3-dicarbonyl compounds with Benzylic alcohols. Initially, Benzhydrol (1a) was chosen as the alkylting agent for the alkylation of acetyl acetone (2a). This model reaction was carried out in dichloromethane at room temperature for 5 min. Complete disappearance of the starting material was observed providing the desired alkylated product 3a in 96% yield (Scheme I).

Scheme I: Alkylation of 1, 3 dicarbonyl compounds



With this positive result, the scope of the work extended for various alcohols and 1, 3-dicarbonyl compounds to obtain the corresponding alkylated products.

General procedure for the alkylation of 1,3-dicarbonyl compounds (3a-m):

A mixture of 1,3-dicarbonyl compound, 2a-2f (1.0 mmol), benzylic alcohol, 1a-1h (1.0 mmol) and Triflic acid (4 mol %) in $CHCl_3$ (10 mL) was stirred at room temperature until the completion of starting material (see Table 1 to 2). The reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography on silica gel to afford pure alkylated 1,3-dicarbonyl compounds 3a-m. The products obtained were characterized by IR, ^1H and ^{13}C NMR and mass spectroscopy.

3.1 Spectral data for the synthesized compounds:

3.1.1 Ethyl 2-benzhydryl-4-chloro-3-oxobutanoate (3d). Colorless solid, M.P.: 118-120 ^oC; IR (KBr): ν_{max} 2976, 1744, 1592, 1494, 1453 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.16 (m, 10H, *Ar-H*), 4.77 (q, *J* = 12.0 Hz, 2 H, CO-*CH*-CO, Ph-*CH*-Ph), 4.06-3.87 (m, 4 H, Cl-*CH*$_2$, O-*CH*$_2$-CH_3), 1.0 (t, *J*= 7.2 Hz, 3 H, *CH*$_3$-CH_2); ^{13}C NMR (75 MHz): δ 195.4, 166.6, 140.9, 140.6, 129.0, 128.6, 127.7, 127.5, 127.2, 127.0, 61.8, 61.4, 50.9, 48.6, 13.6; HRMS (ESI): (*m/z*) calcd for $C_{19}H_{19}ClNaO_3$, 353.0915 $[M+Na]^+$; found, 353.0908.

3.1.2 2-(1,3-Diphenylprop-2-ynyl)-3-hydroxycyclohex-2-enone (**3j).** Colorless solid, M.P.: 170-172 ^oC; IR (KBr): ν_{max} 2953, 1601, 1489, 1450, 1373 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 10.61-10.35 (br s, OH), 7.56-7.38 (m, 4 H, Ar-H), 7.36-7.10 (m, 6 H, Ar-H), 5.57 (s, 1 H, Ph-CH,), 2.62-2.28 (m, 4 H, CO-CH_2, =COH-CH_2), 2.0-1.88 (m, 2 H, CH_2-CH_2-CO): ^{13}C NMR (75 MHz): δ 194.8, 172.2, 140.2, 130.4, 127.1, 126.7, 126.4, 126.2, 124.7, 123.1, 114.8, 89.8, 80.2, 35.5, 29.3, 28.4, 19.5: HRMS (ESI): (*m/z*) calcd for $C_{21}H_{19}O_2$, 303.1380 $[M+H]^+$; found, 303.1391.

3.1.3 3-(Phenyl(1-tosyl-1H-indol-3-yl) methyl)pentane-2,4-dione (3k). White solid, M.P. : 150-153 ^oC.

IR (KBr): ν_{max} 3106, 1737, 1597, 1492, 1447 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$): δ 7.93 (d, *J* = 8.1 Hz, 1 H, Ar-H), 7.66 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.34 (d, *J* = 7.9 Hz, 1 H, Ar-H), 7.27-7.08 (m, 10H, Ar-H, =CH-N), 4.88 (d, *J* = 12.3 Hz, 1 H, Ph-CH), 4.53 (d, *J* = 12.1 Hz, 1 H, CO-CH-CO), 2.34 (s, 3 H, Ts-CH_3), 1.90 (s, 3 H, CH_3-CO), 1.84 (s, 3 H, CH_3-CO); ^{13}C NMR (75 MHz): δ 202.7, 202.4, 144.9, 139.1, 135.3, 134.7, 129.8, 128.8, 128.0, 127.3, 126.7, 125.2, 123.5, 123.1, 119.6, 113.9, 42.4, 31.3, 27.4,

21.5; HRMS (ESI): (*m/z*) calcd for $C_{27}H_{29}N_2O_4S$, 477.1843 $[M+NH_4]^+$; found, 477.1869.

3.1.4 Ethyl 3-oxo-2-(phenyl(1-tosyl-1H-indol -3-yl)methyl) butanoate (3l). Viscous liquid; IR (neat): ν_{max} 3432, 1745, 1599, 1494, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (t, J = 7.2 Hz, 1 H, Ar-H), 7.66 (t, J = 6.6 Hz, 2 H, Ar-H), 7.55-7.04 (m, 11 H, Ar-H, =CH-N), 4.87 (t, J = 12.1 Hz, 1 H, Ph-CH), 4.32 (dd, J =11.7 Hz, 1 H, CO-CH-CO), 3.93 (q, J = 7.2 Hz, 2 H, CH_2-O-CO), 2.34 (s, 3 H, Ts-CH_3), 2.0 (d, J = 21.7 Hz, 3 H, CH_3-CO), 1.02-0.89 (m, 3 H, CH_3-CH_2-O); ^{13}C NMR (75 MHz): δ 201.2, 167.4, 144.8, 139.3, 135.3, 134.8, 129.7, 128.7, 128.5, 128.2, 128.1, 127.2, 126.6, 124.9, 123.4, 123.2, 122.9, 122.1, 119.9, 119.8, 113.8, 113.5, 65.9, 61.5, 30.8, 28.5, 21.5, 13.7; HRMS (ESI): (*m/z*) calcd for $C_{28}H_{27}NNaO_5S$, 512.1502 $[M+Na]^+$; found, 512.1506.

3.1.5 4-(Z)-Acetyl-2-(4-methoxy benzylidene) -5-oxohexanenitrile (3m). Viscous liquid; IR (KBr): ν_{max} 2927, 2208, 1707, 1606, 1514, 1465, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, 2 H, J = 8.7 Hz, Ar-H), 6.90 (d, 2 H, J = 8.9 Hz, Ar-H), 6.72 (s, 1 H, Ar-HC=), 3.84 (s, 3 H, OCH_3), 3.34 (d, 2 H, J = 1.1 Hz, =C-CH_2), 2.17 (s, 6 H, CH_3-CO, CH_3-CO); ^{13}C NMR (75 MHz): δ 192.3, 161.1, 142.2, 130.4, 125.8, 119.0, 114.2, 106.0, 105.0, 55.3, 33.4, 23.2; HRMS (ESI): (*m/z*) calcd for $C_{16}H_{17}NNaO_3$, 294.1101 $[M+Na]^+$; found, 294.1091.

[IV]. DISCUSSION:

The Propargylic benzyl alcohol (1c) and Allylic benzyl alcohol (1b) and were utilized as alkylating agents for the alkylation of (2a) and (2b) to afford the appropriate alkylated products. Dipheylmethanol (1a) on treatment with the derivatives of 1, 3 dicarbonyl compounds (2b), (2c), (2d) results in the respective alkylated moieties. Further, alcohols of different substrates having different groups, such as (1d) and (1e) produces the corresponding alkylated products (3i) and (3m) in prominent yields keeping the protecting groups intact (Table I).

Table1: TfOH-catalized alkylation of 1,3-dicabonylcompounds with benzylic alcohols.

entry	alcohol	1, 3-dicarbyl compound	time (min)	product[a]	yield (%)[b]
1	1a	2b	10	3b	92
2	1a	2c	15	3c	95
3	1a	2d	5	3d	89
4	1a	2e	15	3e	92
5	1b	2a	5	3f	85
6	1b	2b	10	3g	88
7	1c	2a	5	3h	98
8	1c	2b	15	3i	85
9	1c	2f	5	3j	85
10	1d	2a	5	3k	88
11	1d	2b	10	3l	93
12	1e	2a	5	3m	85

[a]All the products were characterized by ^1H, ^{13}C NMR and mass spectra, [b]Isolated yields.

[V]. CONCLUSION:

Developed an adequate method for the alkylation synthesis from 1,3-dicarbonyl compounds with Benzylic alcohol using the reagent Triflic acid, which is commercially available and found as selective and providing the prominent yields.

[VI]. ACKNOWLEDGEMENT:

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[VII]. REFERENCES:

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