TECHNICAL FIELD OF THE INVENTION

The invention relates to a regioselective one step process for synthesis of α-acyloxy carbonyl compounds. The invention particularly discloses a regioselective one step process for synthesis of α-acyloxy carbonyl compounds from alkenes.

BACKGROUND AND PRIOR ART OF THE INVENTION

α-acyloxy carbonyls are often found as the key structural motif for many natural products with interesting biological activities and synthetic therapeutics, refer . P. A. Levine, A. Walti, Org. Synth. Coll. Vol. II 1943, 5. These compounds are the potential starting materials for the pfitzinzer reaction in the synthesis of quinoline salicylic acids and their further functionalization results in various biologically active natural products. The acyl groups can serve as useful protecting groups for the hydroxyl functions in α-hydroxy carbonyls. Their importance is reflected in the extensive synthetic research directed toward introducing acyloxy group in a chemo, regio, stereo and enantioselective manner.

Prior art processes for synthesis of α-acyloxy carbonyls are catalysed by metals, including the direct oxidative coupling of carbonyl compounds with toxic heavy metal oxidants namely $Pb(OAc)_4$, $Tl(OAc)_3$, $Mn(OAc)_3$, thus providing environmentally unfriendly processes, refer Cocker et al, J. Chem. Soc. 1965, 6; M. E. Kuehne, T. C. Giacobbe, J. Org. Chem. 1968, 33, 3359; D. J. Rawilson, G. Sosnovsky, Synthesis 1973, 567; G. J. Williams, N. R. Hunter, Can. J. Chem. 1976, 54, 3830; T. Satoh et al Bull. Chem. Soc. Jpn. 1986, 59, 946 and J. C. Lee, Y. S. Jin, J.-H. Choi, Chem. Commun. 2001, 956, and references therein.

C. S. Beshara, et al in Org.Lett. 2005, 7, 5729, T. Kano, H. Mii, K. Maruoka, J. Am. Chem. Soc. 2009, 131, 3450; M. J. P. Vaismaa, et al Tetrahedron Lett. 2009, 50, 3625 and H. Gotoh, Y. Hayashi, Chem.Commun. 2009, 3083 replaced heavy metal salts with stoichiometric use of N-methyl-Oacylhydroxylamines, but preparation of N-methyl-Oacylhydroxylamines is not an easy process, Also, this is needed in stoichiometric quantities to lead to the desired α-acyloxy carbonyls.

Other prior art processes use harsh conditions for synthesis of desired compounds, making them both economically and environmentally non friendly. Some reports indicate the use of halo substituted carbonyls ie α-halo carbonyls as tarting

materials, which are not commercially available, and therefore will have to be synthesized. This results in long evolving methods of synthesis of desired compounds.

Thus there is a need in the art to provide a simple, environmentally friendly process for synthesis of α-acyloxy carbonyls, such that the process provides a high degree of regio selectivity.

OBJECTIVE OF THE INVENTION

Main objective of the present invention is to provide a one step, one pot process for synthesis of α-acyloxy carbonyls.

Another objective of the invention is to provide a one step, one pot process for synthesis of α-acyloxy carbonyls with high degree of regioselectivity.

One more objective of the invention is to provide an environmentally friendly process conducted in mild conditions with easily available starting compounds.

SUMMARY OF THE INVENTION

In accordance with the objects of the invention, a one step, one pot process for the synthesis α-acyloxy carbonyls with regio selectivity is disclosed, wherein the starting material is an alkene.

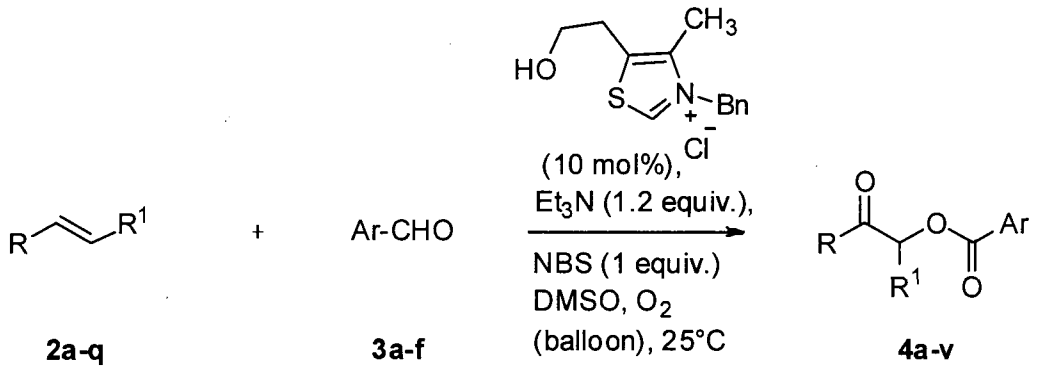
In an embodiment, the process leads to novel α-acyloxy carbonyl compounds that may be used as key structural motif for synthesis of useful, therapeutically active compounds.

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

To accomplish the objectives of the invention, the inventors disclose herein a one step. one pot process comprises reacting alkene (2) and aldehyde (3) in the presence of NHC catalyst (1), N-bromo succinamide (NBS), tri ethyl amine and a solvent, preferably di-methyl sulfoxide (DMSO) in air at temperature 15-30ºC by

stirring for 10-50 hours and isolating product formed. The process is as depicted in Scheme 1.



2a-q

R= H, alkyl, aryl, Bn;
R^1= H, alkyl, aryl, $-CH_2OTBS$, $-CH_2OBn$, -OR, OMOM;

3a-f

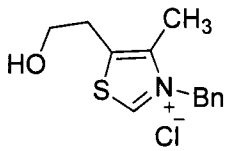
Ar=aromatic, heteroaromatic

4a-v

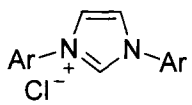
Yield: up to 92%

Scheme 1: NHC catalyzed oxidative functionalization of alkenes with aldehydes.

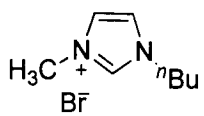
Accordingly, options for N-Heterocyclic carbene catalyst selected from 1a-1f were studied for the synthesis of α-acyloxy carbonyls. In accordance with the results enlisted in table 1, variations of the NHC catalyst 1a-1f yielded the corresponding α-acyloxy carbonyl starting from styrene and 4-NO_2-benzaldehyde.



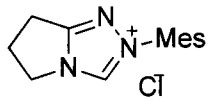
1a



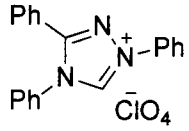
1b Ar = 2,4,6 -$(CH_3)_3C_6H_2$
1c Ar = 2,6 - $iPr_2C_6H_3$



1d



1e



1f

In a preferred embodiment, the NHC catalysts 1a, 1b and 1c and 1d yielded greater than 50% of the α-acyloxy carbonyl.

Table 1- Optimization studies[a] of NHC catalyzed oxidative functionalization of styrene with 4-NO_2-benzaldehyde:

Entry	NHC catalyst	base	solvent	yield (%)[b] of **4a**
1	**1a**	Et_3N	DMSO	92 (81)[c] (46)[d]
2	**1b**	Et_3N	DMSO	65
3	**1c**	Et_3N	DMSO	47
4	**1d**	Et_3N	DMSO	52
5	**1e**	Et_3N	DMSO	14
6	**1f**	Et_3N	DMSO	8
7	**1a**	NaH	DMSO	54
8	**1a**	DBU	DMSO	52
9	**1a**	Cs_2CO_3	DMSO	24
10	**1a**	$KOBu^t$	DMSO	16
11	**1a**	Et_3N	DMSO (5 eq) +THF	15

a: Reaction conditions: styrene (5 mmol), *p*-nitrobenzaldehyde (6 mmol), NHC precatalyst (**1a-1f**) (10 mol%), Base (6 mmol), NBS (5 mmol); all under O_2 atmosphere in DMSO, 25°C, 18 h; b: isolated yield after column chromatographic purification; c: NIS is used instead of NBS; d: NCS is used us halogen source.

Accordingly, the process was worked with options of aldehydes, selected from aromatic and hetero aromatic aldehydes to provide α-acyloxy carbonyl with regio selectivity with yield greater than 70%. Refer Table 2.

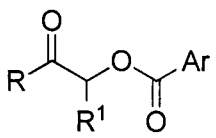
Table 2: NHC catalyzed oxidative functionalization of styrene with aromatic aldehydes[a]

Entry	Aldehydes (**3a-e**)	time (h)	products **(4r-v)**	yield (%)[b] of **(4r-v)**
1	benzaldehyde (**3a**)	38	**4r**	68
2	*m*-tolualdehyde (**3b**)	28	**4s**	81
3	4-Br- benzaldehyde (**3c**)	22	**4t**	78
4	4-Cl- benzaldehyde (**3d**)	24	**4u**	75
5	3-pyridine carboxaldehyde (**3e**)	22	**4v**	73

a: Reaction conditions: styrene (5 m.mol), aromaticaldehyde (5.5 mmol), NHC precatalyst **1a** (10 mol%), Et_3N (5.5 mmol), NBS (5 mmol) in DMSO under O_2 atmosphere; 25°C; b:isolated yield after column chromatographic purification.

Table 3 enlists the various α-acyloxy carbonyls synthesized varying the alkenes (2)., resulting in yield or at least 70% of corresponding α-acyloxy carbonyls.

In an aspect of the invention, the inventors disclose novel α-acyloxy carbonyls of formula 4



R= H, alkyl, aryl, Bn;
R^1= H, alkyl, aryl, -CH_2OTBS,
-CH_2OBn, -OR, OMOM;
Ar=aromatic, heteroaromatic

formula 4

Table 3: NHC catalyzed oxidative functionalization of alkenes with 4-NO_2benzaldehyde[a]

entry	alkenes (**2a-q**)	Time (h)	Products (**4a-q**)	yield (%)[b]
1	styrene (**2a**)	18	**4a**	92
2	4-CH_3-styrene (**2b**)	20	**4b**	77
3	4-Br- styrene (**2c**)	18	**4c**	71
4	4-F- styrene (**2d**)	22	**4d**	79
5	4-OAc- styrene (**2e**)	23	**4e**	82
6	3,4 –$(OMe)_2$ styrene (**2f**)	26	**4f**	74
7	indene (**2g**)	18	**4i**	72
8	stilbene (**2h**)	24	**4j**	81
9	Ph-CH=CH-CH_2-OTBS (**2i**)	28	**4g**	92
10	3,4 –(O-CH_2-O)–Ph-CH=CH -CH_2-OTBS (**2j**)	26	**4h**	81
11	benzyloxy 1-propene (**2k**)	27	**4k**	79
12	1-octene (**2l**)	32	**4l**	71
13	1-decene (**2m**)	29	**4m**	76
14	4-phenyl-1-butene (**2n**)	26	**4n**	74
15	ethoxyethene (**2o**)	30	**4o**	78[c]
16	dihydropyran (**2p**)	28	**4p**	69
17	Ph-CH_2-CH=CH-OCH_2OCH_3 (**2q**)	32	**4q**	73

a: Reaction conditions: alkene (5 mmol), *p*-nitrobenzaldehyde (5.5 mmol), NHC precatalyst **1a** (10 mol%), Et_3N (5.5 mmol), NBS (5 mmol) in DMSO under O_2 atmosphere; 25°C; b:isolated yield after column chromatographic purification; c:reaction was carried out at 0°C.

EXAMPLES

The following examples are given by way of illustration therefore should not be construed to limit the scope of the invention.

Example 1:

General experimental procedure: To a solution of alkenes (**2a-q**) (1equiv.) in DMSO (20 ml), *N*-Heterocyclic carbene (10 mol %), N-Bromo succinamide (1 equiv.), triethyl

amine (1.2 equiv.) and aldehyde (**3a-f**) were added under oxygen atmosphere. The reaction mixture was then stirred at 25°C. After completion (monitored by TLC), the reaction mixture was then concentrated, followed by the addition of H_2O (50 mL). It was extracted with EtOAc (3 x 50 ml) and the combined organic layers dried over anhydrous Na_2SO_4. Removal of solvent gave α-acyloxy carbonyls (**4a-v**), which were purified by column chromatography over silica gel using pet ether/EtOAc (1/19) as eluent to obtain pure α-acyloxy carbonyls in high purity.

Example 2:

2.1. 2-ethoxy-2-oxoethyl 4-nitrobenzoate (4o) (ethoxy ethene as alkene and p-nitro benzaldehyde as aldehyde substrate is used):

^{1}H NMR (200 MHz, CHLOROFORM-*d*) d ppm 1.33 (t, *J*=7.14 Hz, 3 H) 4.28 (q, *J*=7.07 Hz, 2 H) 4.89 (s, 2 H) 8.20 - 8.41 (m, 4 H) **^{13}C NMR** (50 MHz, CHLOROFORM-*d*) d ppm 14.12, 61.57, 123.54, 131.00, 134.56, 163.90, 166.93. **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{11}H_{11}NNaO_6$: 276.0484; found: 276.0489.

2.2. 3-(benzyloxy)-2-oxopropyl 4-nitrobenzoate: (benzyloxy 1-propene as alkene and p-nitro benzaldehyde as aldehyde substrate is used)

^{1}H NMR (200 MHz, CHLOROFORM-*d*) □ ppm 4.21 (s, 2 H) 4.64 (s, 2 H) 5.23 (s, 2 H) 7.37 (s, 5 H) 8.28 (d, *J*=4.29 Hz, 4 H) **^{13}C NMR** (126 MHz, CHLOROFORM-*d*) □ ppm 67.85, 73., 73.94 , 123.55 , 127.92 , 128.32 , 128.66 , 130.99 , 134.66 , 136.55 , 150.78 , 163.88 , 200.84 **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{17}H_{15}NNaO_6$: 352.0797; found: 352.0789.

2.3. 3-((tert-butyldimethylsilyl)oxy)-1-oxo-1-phenylpropan-2-yl 4-bromobenzoate: (Ph-CH=CH-CH_2-OTBS as alkene and p-nitro benzaldehyde as aldehyde substrate is used)

^{1}H NMR (200 MHz, CHLOROFORM-*d*) □ ppm 0.01 (d, *J*=4.42 Hz, 6 H), 0.82 (s, 9 H), 4.18 (d, *J*=5.18 Hz, 2 H), 6.25 (t, *J*=5.18 Hz, 1 H), 7.43 - 7.68 (m, 3 H), 7.95 - 8.07 (m, 2 H), 8.20 - 8.38 (m, 4 H). **^{13}C NMR** (100 MHz, CHLOROFORM-*d*) □ ppm -5.47 ,18.19 , 25.68 , 29.74 , 62.96 , 77.31 , 123.58 , 128.59 , 128.74 , 131.01 , 133.71 ,134.85 ,

135.28 ,150.77 , 163.99 ,194.40. **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{22}H_{27}NO_6SiNa$: 452.1505; found: 452.1517.

2.4. 2-(4-bromophenyl)-2-oxoethyl 4-nitrobenzoate: (4-Br- styrene as alkene and p-nitro benzaldehyde as aldehyde substrate is used)

^{1}H NMR (200 MHz, CHLOROFORM-*d*) □ ppm 5.58 (s, 2 H) 7.67 (m, *J*=8.59 Hz, 2 H) 7.83 (m, *J*=8.46 Hz, 2 H) 8.32 (s, 4 H). **^{13}C NMR** (101 MHz, CHLOROFORM-*d*) □ ppm 66.72 , 96.16 ,) 123.64 , 129.27 , 129.52 , 131.12 , 132.40 , 132.67 , 134.63 , 150.85 , 164.02 , 190.07 . **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{10}BrNNaO_5$: 385.9640; found: 385.9651.

2.5. 2-oxo-2-phenylethyl 4-bromobenzoate: (styrene as alkene and 4-Br - benzaldehyde as aldehyde substrate is used)

^{1}H NMR (200 MHz, CHLOROFORM-*d*) ppm 5.57 (s, 2 H) 7.44 - 7.56 (m, 2 H) 7.57 - 7.68 (m, 3 H) 7.91 - 8.06 (m, 4 H) **^{13}C NMR** (50 MHz, CHLOROFORM-*d*) □ ppm 66.45 , 96.09 , 127.73 , 128.33 , 128.43 , 128.81 , 131.42 , 131.72 , 133.80 , 134.16 ,165.05 , 191.40. **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{11}BrNaO_3$: 340.9789; found: 340.9799.

ADVANTAGES OF THE INVENTION

A new catalytic regio selective method for the preparation of acyloxy carbonyl products in preparative yield from a variety of olefins including aromatic, aliphatic and electron rich at ambient conditions is disclosed. This method is simple, milder and the reagents used are cheap and easy to handle. The process avoids metal catalysts.

Dated this 17 **day of** MAY **2013**

Scientist

Innovation Protection Unit

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