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ARTICLE TYPE

DMSO/I_2 mediated C–C bond cleavage of α-ketoaldehydes followed by C–O bond formation: A metal-free approach for one-pot esterification

Vunnam Venkateswarlu,[a,c] K. A. Aravinda Kumar,[a] Sorav Gupta,[a,c] Deepika Singh,[b,c] Ram A. Vishwakarma,[a,c] Sanghapal D. Sawant[a,c]*

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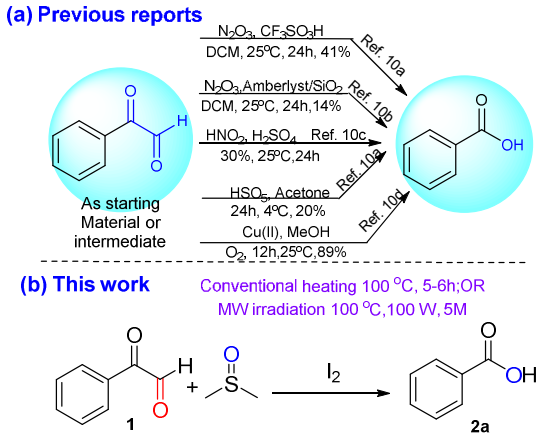
A novel and efficient I_2/DMSO mediated metal-free strategy is presented for the direct C–C bond cleavage of aryl-/heteroaryl- or aliphatic α-ketoaldehydes by C_2-decarbonylation and C_1-carbonyl oxidation to give corresponding carboxylic acids followed by esterification in one-pot, offering excellent yields in both the steps. Here, DMSO acts as oxygen source/oxidant and this reaction works very well under both conventional heating and also under microwave irradiation conditions. This is a very simple and convenient protocol.

Introduction

Dimethyl sulfoxide is an important organic solvent with its proven safety and toxicity profile from the perspective of its biological usage. It is often used as a drug vehicle in *in vivo* and *in vitro* experiments and its extensive use is reported in the literature for various other applications including some medical uses. In organic synthesis, DMSO is known for its versatile applications[1] and is used as a mild oxidant,[2] as illustrated by most popular reactions such as Pfitzner-Moffatt oxidation, the Swern oxidation[3] and many other reactions.[4] Apart from this, there are some other reports for DMSO/iodine mediated oxidation reactions in literature.[5]

There are many methods for the formation of 2-oxoaldehydes including various oxidation procedures of ketones,[6] alkenes[7] and alkynes[8] or directly from diols[9] and many others. However, direct cleavage of carbon-carbon bond of these α-diketo or α-carbonyl carbon bearing compounds is least explored. There are some reports related to direct C–C bond cleavage or on the direct oxidation of α-carbonyl carbon containing compounds. As presented in Scheme 1, there are some reports on oxidation of 2-oxoaldehydes by using some typical procedures/conditions.[10] In these reports, 2-oxoaldehydes are either used as starting material or as intermediate, and then converted to corresponding carboxylic acids. These methods have certain limitations like they require longer time or in some cases the yields are very poor and even some reactions require quite harsh conditions. Apart from these, there are few other reports, in a recent report by Jiao, N., *et. al* carbonyl compounds have been α-hydroxylated by using molecular oxygen which is highly selective for tertiary C(sp^3)–H bond cleavage,[11a] and this group also reported Cu-catalyzed aerobic oxygenation and C–C bond cleavage for obtaining α-ketoesters,[11b] further in another report they achieved the direct hydroxylation of carbonyls using DMSO as oxidant/source of oxygen.[11c] Murata, S., *et. al* reported the air-oxidation of *N,N*-(dialkyl)acylmethylamines to form α-oxoamides along with the formation of benzoic acid.[12] A chemoselective approach has been described by Xihe Bi *et. al* for the direct cleavage of C–C bond of ketones followed by oxidation using CuI and molecular oxygen.[13] In another report by Xuefeng Jiang *et. al* the C–C bonds of α-hydroxy ketones have been cleaved under metal-free aerobic oxidative conditions,[14] the cleavage of carbonyl C–C bond is also described in some other reports.[15] There is still scope for development of new protocols for C–C bond cleavage reactions pertaining to α-carbonyl carbon bond and oxidation of carbonyl carbon.



Scheme 1 (**a**) Reported methods in literature for conversion of 2-oxoaldehydes to carboxylic acid (**b**) Reaction of phenylglyoxal with DMSO and iodine

The selective and direct cleavage of the C–C bond is always challenging for synthetic chemists and also difficult for biologists in certain cases. Much attention in recent years is given by chemists to this concept and it has emerged as one of the major themes in synthetic organic chemistry. In our present study, we

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report simple and efficient strategy for direct $C_1(CO)$–$C_2(CO)$ bond cleavage of 2-oxoaldehydes by oxidation of C_1-carbonyl carbon and C_2-decarbonylation under metal-free conditions using dimethyl sulfoxide and iodine followed by one-pot esterification of obtained carboxylic derivatives with excellent yields.

Results and discussion

In continuation to our interest in development of newer metal-free reactions,[16] present reaction was explored. In a reaction of 2-oxo-2-phenylacetaldehyde **1**, with I_2 in catalytic amount and DMSO as solvent, the decarbonylative oxidation was observed with the formation of benzoic acid **2a**, in low yields (Scheme 1). Therefore, the optimization of reaction was taken up for further improvement in yields and its mechanistic exploitation.

Table 1 Optimization and screening of different reagents for C_1-oxidation of phenylglyoxal using DMSO as solvent at reflux conditions

Entry	Reagent	Quantity (equivalents)	Yield (%)[a]
a.	NaI	1	NR
b.	TBAI	1	NR
c.	NIS	1	30%
d.	NH_4I	1	NR
e.	KI	1	NR
f.	I_2	Catalytic	20%
g.	I_2	0.5	55%
h.	**I_2**	**1**	**95%**
i.	NBS	1	NR
j.	NCS	1	NR

[a]Yields after column purification

In initial studies, the requirement of iodine in the reaction was understood and the reactions using DMSO at reflux conditions were carried out. A reaction conducted without iodine did not undergo. Therefore, it was confirmed that iodine is necessary to perform this conversion. Further, the amount of iodine to be used in the reaction was studied by using catalytic and also with various equivalents of iodine. The reaction with stoichiometric amount of iodine has given the excellent results; exclusive product was observed (Table 1, entry h). To know the generality of iodine source for this reaction, some reagents were screened. But the reaction with the NIS used in stoichiometric amount only gave the product with 30% yields. There was no product formation observed in all other cases (Table 1).

Further in our initial studies, the screening of different solvents was performed to see the role of DMSO solvent and to find the generality for using any other solvent for reaction. The results revealed that only DMSO gave the desired product. The reactions with all other solvents could not convert the substrate to the product (Table 2).

Thus after confirmation of the requirement of DMSO, the next set of experiment was planned; in this, different temperature dependent reactions were performed using DMSO, in which reaction at room temperature has not given the product. However, reactions carried out at 70 °C and 100 °C or at reflux conditions have given the product with 65%, and 95% yields (at 100 °C and reflux both) respectively. To our observations, reaction at 100 °C was found to be the best condition. This reaction was then subjected under microwave irradiation, which went smoothly and was found to be a convenient protocol for generation of more number of examples.[17] The conditions were optimized under microwave for obtaining higher yields of the product. In optimization, the reaction conducted using 100 Watt of MW power at 180 °C led to give best results (>95% yield). Therefore, all subsequent reactions were then performed using this condition. Interestingly, in our further studies on understanding the mechanism part of this reaction, it was observed that DMSO plays an essential role as the source of oxygen, which is described later in detail.

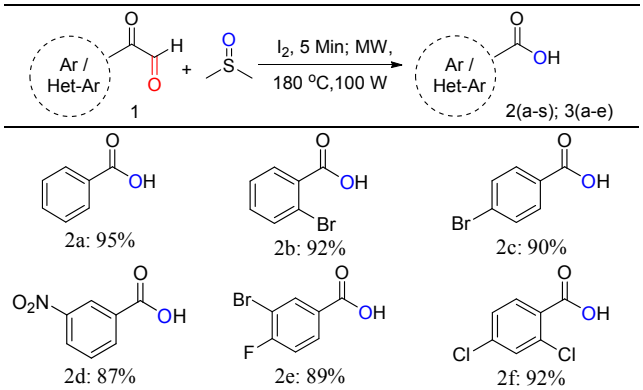
Table 2 Screening of different solvents for oxidation of phenylglyoxal for formation of benzoic acid

Entry	Solvent	Temp. (°C)	Time	2a; Yield (%)[a]
	Conventional Heating Conditions			
a.	DMSO	189	6 hr	95%
b.	DMSO	RT	6 hr	NR
c.	DMSO	70	6 hr	65%
d.	**DMSO**	**100**	**6 hr**	**95%**
e.	H_2O	100	6 hr	NR
f.	MeOH	65	6 hr	NR
g.	DMF	153	6 hr	NR
h.	1,4-Dioxane	101	6 hr	NR
i.	THF	66	6 hr	NR
j.	MeCN	82	6 hr	NR
k.	$CHCl_3$	61	6 hr	NR
	Under Microwave Irradiation Conditions			
a.	DMSO	100 at 80 W	5 Min	NR
b.	DMSO	100 at 100 W	5 Min	25%
c.	DMSO	150 at 100 W	5 Min	85%
d.	**DMSO**	**180 at 100 W**	**5 Min**	**95%**

[a]Yields are based on GC-MS analysis; NR: No Reaction; RT: room temperature

With the optimal conditions in hand, a series of aryl-2-oxoaldehydes were investigated to evaluate the generality of this reaction (Table 3). In general, both electron-withdrawing and -donating substitutions could be accommodated and successfully converted to the corresponding carboxylic acids with excellent yields. Adding the substituted group at different positions on the aryl ring of 2-oxoaldehydes had no obvious influence on the yields. The different examples of aryl glyoxals are presented in Table 3.

Table 3 Synthesis of different aryl-carboxylic acids from aryl/heteroaryl glyoxals using DMSO/I_2[a]



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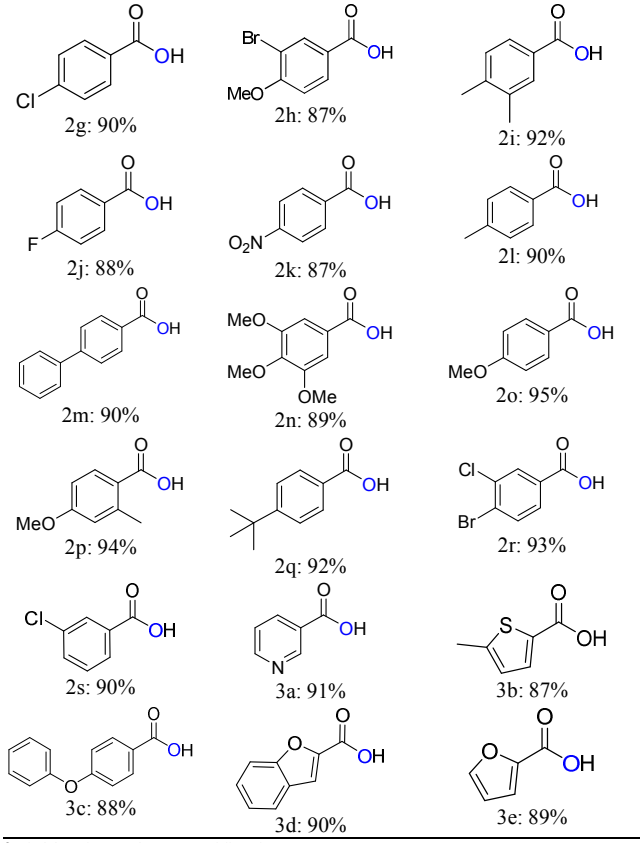
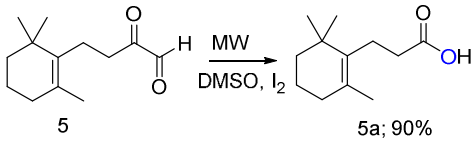


[a]Yields after column purification

However, to know the applicability of present reaction on the heteroaryl substrates, the reaction with various heteroaryl glyoxals were investigated. All the substrates have given good yields of corresponding carboxylic acids derivative as shown in table 3.

To know the applicability of this reaction on aliphatic α-ketoaldehydes, a typical reaction on the 2-oxo-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butanal was carried out, which gave the desired 3-(2,6,6-trimethylcyclohex-1-en-1-yl)propanoic acid, commonly called β-ionic acid (Scheme 2).



Scheme 2 Example showing application of DMSO/I_2 mediated C–C cleavage in aliphatic glyoxal; substrate 5 is converted to corresponding β-ionic acid 5a.

From mechanistic perspective and for understanding the role of DMSO and iodine, we envision the following plausible pathway for present reaction. DMSO is well reported in literature to provide oxygen or as oxidant, as discussed earlier. As observed in our initial experiments, the reaction in other solvents has not given the desired product; this shows the presence of DMSO is required to undergo the reaction. Also, presence of iodine is required to undergo this reaction, as can be seen from the results described in table 1, which can be supported by the evidence that only the product was observed with NIS in our initial screening of reagents, indicating the requirement of iodonium ion, which plays crucial role in moving the reaction forward. Thus, iodonium ion is essential, which initiates the reaction and forms the desired product. From careful analysis and our hypothesis as presented in fig. 1, in the first step, iodine interacts with oxygen of -CHO group followed by nucleophilic addition of oxygen atom of DMSO. This intermediate is stabilized by DMSO molecues[4b,c] and forms intermediate **3**, its subsequent iodination at alpha position of carbonyl gives iodinated intermediate **4**, which later forms **5**. The intermediate **5** (C_1O group) interacts with iodine molecule further to give **6**, followed by the nuclophilic addition of DMSO molecule that leads to the formation of intermediate **7**, which is stabilized by DMSO molecules. This intermediate **7** releases carbon dioxide (CO_2) and dimethyl sulfide (DMS) and forms intermediate **8**. After protonation this intermediate forms the desired benzoic acid **2a** by the release of dimethyl sulfide and iodonium ion.[11c]

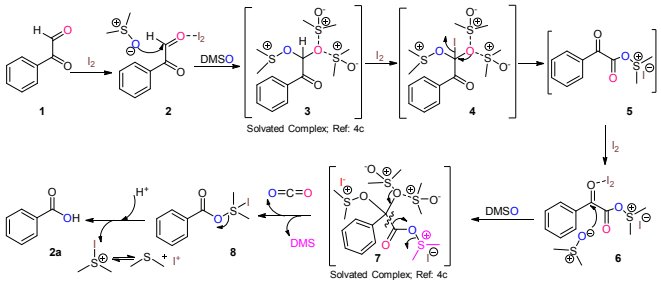


Fig. 1 Plausible mechanism of oxidation of 2-oxoaldehydes by C–C bond cleavage using DMSO as source of oxygen in presence of iodine

To support our hypothesis, we conducted an ESI-MS experiment (Figure 1S(A to E), in ESI), in a reaction with an example of 2-(4-methoxyphenyl)-2-oxoacetaldehyde **1b**, the samples were collected during the progress of reaction at regular interval. In the observation, the intermediates were analyzed and identified as presented in the fig. 1S[A] (in ESI) and product formation **2b**, after completion of reaction as can be seen in 1S[B] (in ESI). Further the desired fragmentation pattern was also observed for the intermediate, as can be seen in the GC-MS for this substrate **1b**, as shown in fig. 1S[C], [D], and [E] (in ESI). Moreover, to confirm this route and to rule out the possibility of involvement of air oxygen in oxidation process, the reactions were performed under inert and anhydrous atmospheric conditions without using DMSO, where the required product was not observed.

Further extension of the method was planned and the esterification using one-pot method was carried out under microwave irradiation conditions. Wherein, we obtained the desired products in excellent yields (>70%), all the reactions went smoothly. Some of the representative examples are presented in table 4.[18] In an optimization studies, after first step the crude material of carboxylic acid was used as such in a same spot and addition of corresponding alcohol led to formation of ester. After carrying some optimization reactions, the best results were obtained at 80 °C using 80 Watt microwave power for maintaining the reaction up to 3 minutes.

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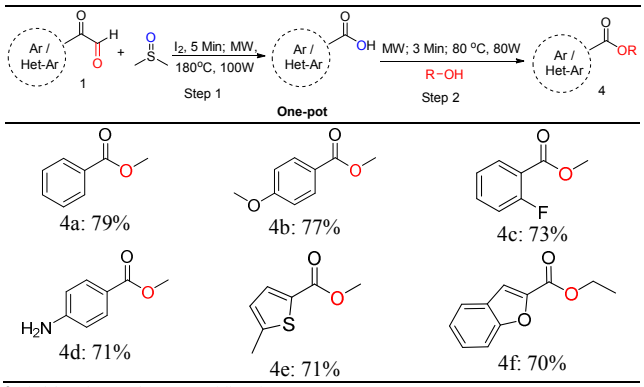
Table 4 Examples of esters prepared by present method using two steps in one-pot [a]



[a]Yields after column purification

Experimental

General information: All reactions were performed in inert conditions under nitrogen/argon atmosphere. The reactions are conducted in conventional heating conditions and also using microwave irradiation (CEM-Discover make Microwave Synthesizer), under sealed atmosphere. Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F254 (20 x 20 cm). TLC plates were visualized by exposing UV light or by iodine vapors or immersion in an acidic staining solution of *p*-anisaldehyde followed by heating on hot plate. Organic solvent were concentrated by using BUCHI rotary evaporator and dried using high capacity vacuum pump. Flash column chromatography was performed on flash silica gel 230-400 mesh size. ^{1}H NMR spectra were recorded with 400 and 500 MHz BRUCKER NMR instruments. Chemical data for protons are reported in parts per million (ppm scale) downfield from tetramethylsilane and are referenced to the residual proton in the solvent ($CDCl_3$, DMSO-d6, Acetone-d6 or other solvents as mentioned). Mass spectra were recorded with Agilent's ESI-MS and GC-MS instrument from Thermo Scientific.

(A) *General procedure for the preparation of acids using conventional heating method*: In a typical procedure, the mixture of phenylglyxol (100 mg, 0.66 mol), iodine (167.6 mg, 0.66 mol) in dimethyl sulfoxide (1 ml) was heated at 100 °C. The progress of reaction was monitored by TLC. After completion of the reaction, saturated hypo solution was added to the reaction mixture and compound was extracted with ethylacetate (2x20 ml). The organic layer was separated and concentrated under reduced pressure. Purification was performed using silica-gel column chromatography.

(B) *General procedure for the preparation of acids using microwave conditions*: In a typical procedure, the mixture of phenylglyxol (100 mg, 0.66 mol), iodine (167.6 mg, 0.66 mol) in DMSO (1ml) were placed in a 10 mL crimp-sealed thick-walled glass tube, especially made for MW reactions, equipped with a pressure sensor and a magnetic bead for stirring. This reaction tube was placed in a CEM-Discover Microwave synthesizer and operated at 180 °C using a power of 100 W for 5 min. After completion of the reaction, the organic portion was extracted into ethyl acetate and evaporated the organic solvent under reduced pressure on rotary evaporator. Crude was purified on silica gel chromatography by the ratio of hexane and ethylacetate as eluent afforded the product, benzoic acid[17a,b] (2a) in 95% yield. ^{1}H NMR (400 MHz, MeOD) δ 8.03 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H). 13C NMR (101 MHz, MeOD) δ 170.0, 134.1, 131.8, 130.8, 129.5; (+) ESI-MS: 145.1 (M+ + Na).

(C) *General procedure for the preparation of esters under microwave conditions*: In a typical procedure, the mixture of 4-aminophenylglyoxal (100 mg, 0.67 mol), iodine (170.3 mg, 0.67 mol) in DMSO (1ml) were placed in a 10 mL crimp-sealed thick-walled glass tube, especially made for MW reactions, equipped with a pressure sensor and a magnetic bead for stirring. This reaction tube was placed in a CEM-Discover Microwave synthesizer and operated at 180 °C using a power of 100 W for 5 min. After completion of the reaction, 4-amino benzoic acid as such, as crude was used for next step, which is followed by the addition of *para*-toluene sulfonic acid (*p*-TSA, 0.1 eq) and MeOH (1 ml). This reaction mixture was maintained under microwave conditions (80 °C, 80W for 5 min). After completion of the reaction saturated hypo ($Na_2S_2O_3$) solution was added to the reaction mixture. The reaction mixture was diluted with ethylacetate and the organic layer was separated and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure. The crude material was purified by silica gel chromatography by using hexane: ethylacetate (8:2) as eluent afforded the product methyl 4-aminobenzoate (4d)[18a] with 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 4.15 (s, 2H), 3.84 (s, 3H); (M+).13C NMR (126 MHz, $CDCl_3$): δ 167.28, 151.02, 131.61, 119.52, 113.79, 51.64. GC-MS:151.1

Conclusions

In conclusion, we have developed a simple and efficient method for the C–C bond cleavage followed by oxidation of C_1(CO)-carbon of 2-oxoaldehydes to form carboxylic acids with excellent yields in the presence of dimethyl sulfoxide and iodine and further in next step it forms ester in one-pot. The method finds its scope for converting different 2-oxoaldehyde substrates to corresponding carboxylic acids and esters. The method offers wide substrate scope and is also useful on alkyl as well as heteroaryl substrates.

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Notes and references

[a]*Medicinal Chemistry Division,* [b]*QC-QA Division, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-180 001, India and* [c]*Academy of Scientific and Innovative Research, Anusandhan Bhawan, 2 Rafi Marg, New delhi-110 001, India. Fax: +91191 2586333; Tel: +911912585222; E-mail: sdsawant@iiim.res.in ; sawant.rrl@gmail.com ; IIIM communication no.: IIIM/1781/2015*

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