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Metal-Free Csp^3–N Bond Cleavage of Amides Using *tert*-Butyl Hydroperoxide as Oxidant

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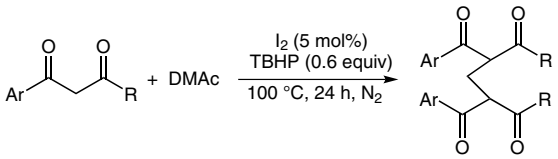

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Abstract A mild and efficient protocol for the metal-free C–N bond-cleavage of amides has been developed. The methodology employs iodine as a catalyst to cleave the C(Me)–N bond of dimethylformamide or dimethylacetamide, providing novel access to methylene-bridged bis-1,3-dicarbonyl compounds instead of enol carbamates in the presence of *tert*-butyl hydroperoxide.

Key words metal-free, C–N bond cleavage, amides, dicarbonyl compounds, oxidation

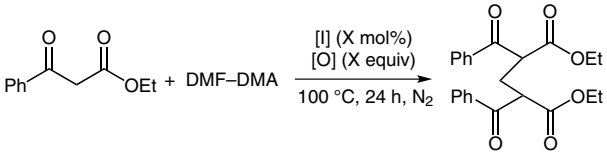
Amides such as dimethylformamide (DMF) and dimethylacetamide (DMA) are not only commonly utilized solvents in organic chemistry, they are also significant reagents in organic synthesis industry.[1] For instance, DMF provides a CHO group for aryl compounds through the cleavage of the C–N bond in the Vilsmeier–Haack reaction.[2] DMF can also serve as an amino source in C–H amination of benzoxazoles, pyrazinones, and others.[3] Amides can also be employed as a CN source in cyanation reactions.[4] Recently, extensive efforts have been directed toward the cleavage of Csp^3–N bonds of DMF or DMA. In 2012, Xu developed an iron-catalyzed benzylic vinylation between 2-methyl azaarenes and DMA or DMF.[5] At the same time, Wang reported an iron-catalyzed sp^3 C–H functionalization of 2-methyl quinolones by using DMF as carbon source in the presence of *tert*-butyl hydroperoxide (TBHP).[6] More recently, Xue and Xiao disclosed an α-methylation of ketones with DMF using Rh salt as catalyst.[7] Miura developed a copper-catalyzed methylenation of benzylpyridines by using DMA as the carbon source.[8] Meanwhile, Lei developed a methylenation of 1-aryl-pyridinemethanes/arylketones and DMF under oxidative conditions.[9] Among the reactions mentioned above, transition-metal catalysts were generally necessary. Herein, we report on the metal-free Csp^3–N bond-cleavage of DMA and DMF by utilization of I_2 as the catalyst.

The synthesis of methylene-bridged compounds has received increasing attention in recent years. Among the previous reports, tertiary amines served as a carbon source through metal-catalyzed cross-dehydrogenative coupling (CDC) reaction. Common solvents were rarely utilized as a carbon source except for a recent example, in which nitromethane severed as a carbon source under the catalysis of $AuCl_3$ or $Cu(OTf)_2$.[10] Very recently, we developed a metal-free methylenation of β-keto esters and diketone with *N*,*N*,*N*,*N*-tetramethylethane-1,2-diamine (TMEDA) severing as the carbon source.[11] Therefore, in a continuation of our efforts in this field, β-keto esters were chosen as the reaction partner to accept the C–N bond-cleavage fragment of DMF or DMA. This reaction system has been reported to proceed in the present of a copper catalyst.[12]

Initially, ethyl 3-oxo-3-phenylpropanoate and DMF were chosen as the model substrates to optimize the reaction conditions. As summarized in Table 1, the reaction gave a trace amount of the desired product without catalyst using $K_2S_2O_8$ as the oxidant at 100 °C for 24 h under a nitrogen atmosphere (Table 1, entry 1). In the presence of KI (20 mol%), the reaction provided **2a** in encouraging yield (13% yield; entry 2). Further screening of a range of iodine species revealed I_2 to be superior, forming **2a** in 18% yield (entries 3 and 4).

When hypervalent iodine reagents such as ICl and $PhI(OAc)_2$ were used as catalysts, no product was detected, which indicates that the reaction does not proceed through a hypervalent iodine mediated process (Table 1, entries 5 and 6). When DMA was employed as the reaction partner, the reaction proceeded more efficiently than with DMF, providing **2a** in 29% yield (entry 7). Therefore, various oxidants were screened to improve the yield with DMA as the carbon source. When using an aqueous solution of TBHP, the reaction resulted in an enhanced yield (45% yield; entry 8). Use of the oxidant BQ or TEMPO gave the desired product in 41 or 30% yields, respectively (entries 9 and 10). However, other oxidants such as DTBP, Oxone, DDQ, BPO, and CAN or more environmentally friendly oxidants such as air and O_2, were found to be ineffective in the catalysis of

Table 1 Screening the Reaction Conditions[a]



1a **2a**

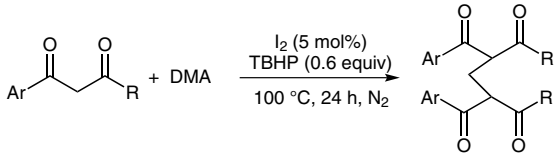
Entry	Catalyst	Solvent	Oxidant	Yield (%)[b]
1	–	DMF	$K_2S_2O_8$	trace
2	KI	DMF	$K_2S_2O_8$	13
3	NIS	DMF	$K_2S_2O_8$	15
4	I_2	DMF	$K_2S_2O_8$	18
5	ICl	DMF	$K_2S_2O_8$	–
6	$PhI(OAc)_2$	DMF	$K_2S_2O_8$	–
7	I_2	DMA	$K_2S_2O_8$	29
8	I_2	DMA	TBHP	45
9	I_2	DMA	BQ	41
10	I_2	DMA	TEMPO	30
11	I_2	DMA	DTBP	trace
12	I_2	DMA	Oxone	trace
13	I_2	DMA	DDQ	trace
14	I_2	DMA	CAN	trace
15	I_2	DMA	BPO	–
16	I_2	DMA	O_2	trace
17	I_2	DMA	air	trace
18[c]	I_2	DMA	TBHP	39
19[d]	I_2	DMA	TBHP	27
20[e]	I_2	DMA	TBHP	55
21[f]	I_2	DMA	TBHP	40
22[g]	I_2	DMA	TBHP	61
23[h]	I_2	DMA	TBHP	24

[a] Reaction conditions: **1a** (0.5 mmol), cat. (20 mol%), oxidant (1.2 equiv), DMF–DMA (2.0 mL), 100 °C, 24 h, N_2 atmosphere; BPO = benzoyl peroxide.
[b] Isolated yield.
[c] 120 °C.
[d] 80 °C.
[e] TBHP (0.6 equiv).
[f] TBHP (2.0 equiv).
[g] I_2 (5 mol%).
[h] I_2 (1 mol%).

this transformation (entries 10–17). Evaluation of the effect of temperature and the loading of TBHP suggested that performing the reaction at 100 °C and with 0.6 equiv. of oxidant was effective (entries 18–21). A decrease in the catalyst loading from 20 to 5 mol% improved the yield of **2a** to 61%, whereas a further decrease in catalyst loading to 1 mol% did not benefit the transformation (entries 21–22). The decrease in the loadings of both oxidant and catalyst may avoid the oxidation of the β-keto esters, which might account for the elevation in the yield.[13]

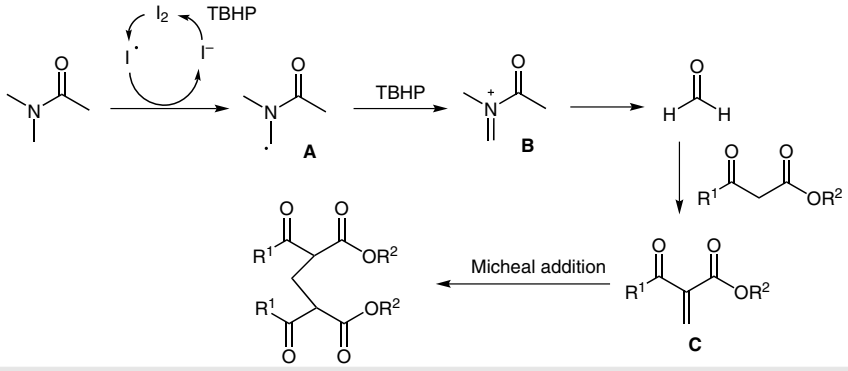
With the optimized reaction conditions in hand, we next investigated the scope and limitations of this transformation. As summarized in Table 2, 1b gave the desired product **2b** in an isolated yield of 47% under the optimal conditions (entry 2). The nature of the substitutes on the benzene ring was examined, and the results showed that the electronic effect was not significant; electron-withdrawing groups such as NO_2 resulted in formation of the corresponding product with 41% yield, and groups such as 4-bromo, 4-chloro, and 4-fluoro on the benzene ring also giving moderate yields (entries 3–6). Substrates bearing an electron-donating group on the phenyl ring such as 4-Me and 4-MeO were also transformed into the corresponding product **2g** and **2h** in moderate yield under the same conditions (entries 7 and 8). Application of substrate **1i**, with 3-MeO group on the benzene, also proceeded, giving the desired product in 43% yield (entry 9). 2-Nathyl and 4-morpholino substituted substrates gave **2g** and **2h** in 53 and 50% yields, respectively (entries 10 and 11). β-Keto amides such as **1l** could also undergo this reaction, affording the

Table 2 Reaction Scope[a]



Entry	Ar	1	R	Yield (%)[b]	*dr*
1	Ph	**1a**	OEt	61 (**2a**)	1.1:1
2	Ph	**1b**	OMe	47 (**2b**)	6:5
3	4-$O_2NC_6H_4$	**1c**	OEt	41 (**2c**)	1.1:1
4	4-BrC_6H_4	**1d**	OMe	51 (**2d**)	1.3:1
5	4-ClC_6H_4	**1e**	OMe	59 (**2e**)	1.3:1
6	4-FC_6H_4	**1f**	OMe	50 (**2f**)	4:3
7	4-MeC_6H_4	**1g**	OMe	51 (**2g**)	1:1
8	4-$MeOC_6H_4$	**1h**	OMe	57 (**2h**)	1.1:1
9	3-$MeOC_6H_4$	**1i**	OMe	43 (**2i**)	5:4
10	2-naphthyl	**1j**	OMe	53 (**2j**)	1.3:1
11	4-morpholinophenyl	**1k**	OMe	50 (**2k**)	1:1
12	Ph	**1l**	morpholino	30 (**2l**)	6:5
13	Ph	**1m**	Ph	0 (**2m**)	
14	Me	**1n**	OEt	0 (**2n**)	

[a] Reaction conditions: **1a** (0.5 mmol), I_2 (5 mol%), DMA (2 mL), TBHP (70% aq; 45.0 μL), 100 °C, 24 h, N_2 atmosphere.
[b] Isolated yield.



Scheme 1 Proposed mechanism for C–N cleavage of DMA for the synthesis of bridged bis-1,3-dicarbonyl compounds

desired product **2l** in 30% yield (entry 12). Unfortunately, the diketone and alkyl β-keto ester did not undergo the reaction (entries 13 and 14).

The exact mechanism for the C–N cleavage of amides is still not clear; however, a proposed mechanism is illustrated in Scheme 1. Firstly, iodine radical is generated through a hemolytic reaction. Secondly, a radical relay occurs between the iodine radical and DMA to produce radical **A**, which undergoes oxidation mediated by TBHP to afford imine ions **B**. The latter undergoes hydrolysis to generate formaldehyde, which is followed by an aldol reaction with β-keto esters to form intermediate **C**. Finally, nucleophilic attack of the β-keto esters on intermediate **C** affords to the target products.[5,9]

In summary, a metal-free C–N cleavage of DMF and DMA has been demonstrated.[14] Methylene-bridged compounds were obtained with moderate yields by using β-keto esters as the fragment acceptor under the oxidative conditions. Screening of the substrate scope showed that the electronic effect of substituents onto the benzene ring was weak. Further extension of the substrate scope and study of the mechanism of this type of C–N cleavage are under investigation in this lab.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379879.

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(14) **Preparation of 2a; Typical Procedure:** A mixture of ethyl 3-oxo-3-phenylpropanoate (0.5 mmol), iodine (6.4 mg, 0.025 mmol), DMA (2.0 mL), and 70% TBHP (32.0 µL) was stirred at 100 °C for 24 h under an N_2 atmosphere. The reaction was monitored by TLC. Upon completion, the reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 × 15 mL). The organic phase was concentrated and the resulting crude product was purified by column chromatography on silica gel (petroleum ether–EtOAc, 10:1) to provide the desired compound. The identity of the product and the diastereomer ratio were determined by 1H NMR analysis.

Diethyl 2,4-dibenzoylpentanedioate (2a): Yield: 61%; two diastereomers (1.1:1). ^{1}H NMR (601 MHz, $CDCl_3$): δ = 8.06–8.05 (m, 4 H), 7.62–7.61 (m, 2 H), 7.52–7.46 (m, 4 H), 4.64 (t, *J* = 7.2 Hz, 1 H), 4.55 (t, *J* = 7.2 Hz, 1 H), 4.24–4.21 (m, 2 H), 4.11–4.09 (m, 2 H), 2.78–2.52 (m, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.11 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.29, 194.92, 169.80, 169.44, 135.95, 135.46, 133.93, 133.92, 129.01, 128.92, 61.77, 61.75, 51.65, 51.39, 28.30, 27.75, 14.10, 13.97.

Dimethyl 2,4-dibenzoylpentanedioate (2b): Yield: 47%; two diastereomers (6:5). ^{1}H NMR (601 MHz, $CDCl_3$): δ = 8.05 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 4 H), 7.63–7.58 (m, 2 H), 7.52–7.47 (m, 4 H), 4.67 (t, *J* = 7.2 Hz, 1 H), 4.58 (t, *J* = 7.2 Hz, 1 H), 3.75 (s, 4 H), 3.64 (s, 2 H), 2.77–2.55 (m, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.22, 194.82, 170.33, 169.93, 135.89, 135.42, 134.05, 134.03, 129.08, 129.01, 128.98, 128.87, 52.78, 51.41, 51.16, 28.47, 27.93.

Diethyl 2,4-bis(4-nitrobenzoyl)pentanedioate (2c): Yield: 41%; two diastereomers (1.1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.37 (m, 4 H), 8.20–8.25 (m, 4 H), 4.66 (t, *J* = 8.0 Hz, 1 H), 4.55 (t, *J* = 8.0 Hz, 1 H), 4.21–4.25 (m, 2 H), 4.11–4.14 (m, 2 H), 2.54–2.79 (m, 2 H), 1.21 (t, *J* = 8.0 Hz, 3 H), 1.11 (m, 3 H).

Dimethyl 2,4-bis(4-bromobenzoyl)pentanedioate (2d): Yield: 51%; two diastereomers (1.3:1). ^{1}H NMR (601 MHz, CDCl3): δ = 7.94–7.88 (m, 4 H), 7.67–7.60 (m, 4 H), 4.59 (t, *J* = 7.2 Hz, 1 H), 4.50 (t, *J* = 7.2 Hz, 1 H), 3.75 (s, 4 H), 3.64 (s, 2 H), 2.72–2.51 (m, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 194.23, 193.82, 170.05, 169.61, 134.60, 134.17, 132.41, 130.55, 130.45, 129.59, 129.53, 52.92, 51.24, 51.08, 28.24, 27.64.

Dimethyl 2,4-bis(4-chlorobenzoyl)pentanedioate (2e): Yield: 59%; two diastereomers (1.3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 4 H), 7.47 (t, *J* = 8.8 Hz, 4 H), 4.60 (t, *J* = 7.2 Hz, 2 H), 3.75 (s, 6 H), 2.73–2.50 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.03, 170.09, 140.78, 133.72, 130.50, 129.40, 73.08, 52.98, 51.29, 28.30.

Dimethyl 2,4-bis(4-fluorobenzoyl)pentanedioate (2f): Yield: 50%; two diastereomers (4:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.08 (m, 4 H), 7.20–7.14 (m, 4 H), 4.63 (t, *J* = 8.0 Hz, 1 H), 4.53 (t, *J* = 8.0 Hz, 1 H), 3.76 (s, 4 H), 3.65 (s, 2 H), 2.75–2.50 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.70, 193.22, 170.25, 169.74, 167.67, 165.12, 131.98, 131.88, 116.35, 116.14, 52.90, 51.31, 51.08, 28.45, 27.77.

Dimethyl 2,4-bis(4-methylbenzoyl)pentanedioate (2g): Yield: 51%; two diastereomers (1.2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.0 Hz, 4 H), 7.27 (d, *J* = 8.0 Hz, 4 H), 4.52–4.64 (m, 2 H), 3.74 (s, 5 H), 3.63 (s, 1 H), 2.74–2.52 (m, 2 H), 2.42 (d, *J* = 8.8 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.82, 170.44, 145.03, 132.99, 129.68, 129.21, 52.72, 51.36, 28.59, 21.85.

Dimethyl 2,4-bis(4-methoxybenzoyl)pentanedioate (2h): Yield: 57%; two diastereomers (1.1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.8 Hz, 4 H), 6.99–6.93 (m, 4 H), 4.60 (t, *J* = 7.2 Hz, 1 H), 4.52 (t, *J* = 7.6 Hz, 1 H), 3.89 (d, *J* = 7.6 Hz, 6 H), 3.75 (s, 3 H), 3.64 (s, 3 H), 2.75–2.51 (m, 2 H). 13C NMR (101 MHz, $CDCl_3$): δ = 193.79, 193.34, 170.63, 170.17, 164.29, 131.57, 131.47, 128.92, 128.41, 114.20, 55.70, 55.68, 52.71, 51.25, 50.96, 28.86, 28.20.

Dimethyl 2,4-bis(3-methoxybenzoyl)pentanedioate (2i): Yield: 43%; two diastereomers (5:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.61 (m, 2 H), 7.57 (s, 2 H), 7.39 (dt, *J* = 16.8, 8.0 Hz, 2 H), 7.19–7.09 (m, 2 H), 4.63 (t, *J* = 7.2 Hz, 1 H), 4.54 (t, *J* = 7.2 Hz, 1 H), 3.88 (d, *J* = 8.8 Hz, 6 H), 3.75 (s, 3 H), 3.64 (s, 3 H), 2.77–2.53 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.08, 194.64, 170.31, 169.93, 160.14, 160.11, 137.19, 136.71, 130.00, 121.70, 121.58, 120.96, 120.85, 55.65, 52.80, 52.78, 51.61, 51.34, 28.65, 28.08.

Dimethyl 2,4-di(2-naphthoyl)pentanedioate (2j): Yield: 53%; two diastereomers (1.3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 12.0, 2 H), 8.12 (d, *J* = 20.0 Hz, 2 H), 8.05–8.02 (m, 2 H), 7.94–7.92 (d, *J* = 8.0 Hz, 2 H), 7.89–7.82 (m, 3 H), 7.65–7.49 (m, 4 H), 4.85 (t, *J* = 8.0 Hz, 1 H), 4.79 (t, *J* = 8.0 Hz, 1 H), 3.78 (s, 3 H), 3.64 (s, 3 H), 2.93–2.69 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.22, 194.74, 170.36, 170.06, 136.04, 135.97, 133.21, 132.78, 132.65, 132.56, 131.43, 131.25, 130.08, 130.04, 129.15, 129.08, 128.91, 128.85, 127.89, 127.79, 127.10, 126.98, 124.20, 124.11, 52.87, 52.81, 51.46, 51.33, 28.83, 28.24.

Dimethyl 2,4-bis(4-morpholinobenzoyl)pentanedioate (2k): Yield: 50%; two diastereomers (1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 9.2 Hz, 4 H), 6.87 (dd, J = 12.8, 8.8 Hz, 4 H), 4.58 (t, *J* = 7.2 Hz, 1 H), 4.50 (t, *J* = 7.2 Hz, 1 H), 3.85 (d, *J* = 3.6 Hz, 8 H), 3.74 (s, 3 H), 3.63 (s, 3 H), 3.35–3.32 (m, 8 H), 2.74–2.50 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 193.27, 192.82, 170.82, 170.34, 154.68, 154.66, 131.28, 131.20, 126.28, 125.75, 113.30, 66.56, 52.53, 51.09, 50.69, 47.30, 29.01, 28.33.

2,4-Dibenzoyl-1,5-dimorpholinopentane-1,5-dione (2l): Yield: 30%; two diastereomers (6:5). ^{1}H NMR (601 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.8 Hz, 1 H), 8.12–8.08 (m, 3 H), 7.63 (t, *J* = 7.2 Hz, 1 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.54 (t, *J* = 7.8 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 3 H), 4.90–4.84 (m, 2 H), 3.74–3.56 (m, 16 H), 2.75–2.25 (m, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 196.32, 196.25, 168.70, 168.65, 135.61, 135.41, 134.01, 129.21, 129.16, 128.68, 66.87, 66.76, 66.67, 49.56, 49.52, 46.49, 46.36, 42.67, 42.55, 29.06, 28.94