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Solvent-free silica gel mediated decarboxylation of C–O coupling products of β-diketones and β-oxo esters with malonyl peroxides

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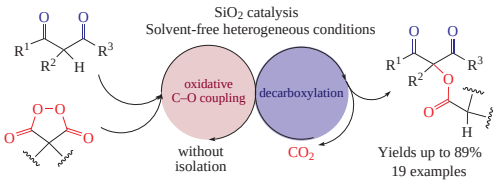
Silica gel was found to mediate decarboxylation of tetracarbonyl compounds with a free carboxylic group prepared from β-dicarbonyl compounds and malonyl peroxides. Under solvent-free heterogeneous conditions silica gel effectively acts as a mediator of C–O coupling with further decarboxylation at 120 °C.

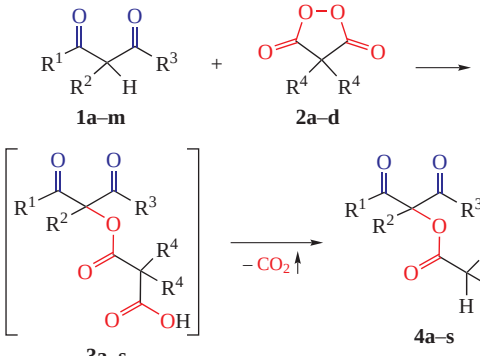


This work covers two important fields: new methodology for decarboxylation with the use of cheap, available, and reusable silica gel[1–3] and selective C–O bond formation in reaction of carbonyl compounds with peroxides.[4–10] Previously[11] we described silica gel mediated synthesis of tetracarbonyl compounds *via* selective oxidative C–O bond formation in reaction of β-dicarbonyl compounds with diacyl peroxides.[12–14] Silica gel and relative materials are widely applied in various industries, including chemical and medical.[15,16] Variety of silica gel applications is based on its availability, stability to heating, and possibility of recycling without significant changes in properties.[17]

Herein, we report on one-pot silica gel mediated synthesis of tetracarbonyl compounds with a free carboxylic group followed by decarboxylation leading to α-acyloxy derivatives of the starting β-dicarbonyl compounds. Decarboxylation of α,α-disubstituted malonic acid monoesters is not trivial due to their reluctance. The approaches to carrying out such a process are scantily presented in the literature. For decarboxylation of related to this work disubstituted malonic monoesters hard conditions (160–200 °C, 0.1–10 Torr),[18,19] biochemical approach[20] or microwave irradiation[21] were applied.

Reaction between β-dicarbonyl compounds **1** and malonyl peroxides **2** brought about tetracarbonyl compounds **3** with selective oxidative C–O bond formation (Scheme 1). Their subsequent *in situ* decarboxylation was performed in heterogeneous SiO_2-containing system without solvent and resulted in products **4a–s**.

We started investigations of heterogeneous SiO_2-containing system for decarboxylation using the model reaction of β-oxo ester **1j** and malonyl peroxide **2a**. The influence of type of silica gel, its amount, temperature and reaction time on the yield of products **3j** and **4j** was estimated (Table 1). A crucial role of silica gel in the formation of compounds **3j** and **4j** was shown (entries 1–3). The product of oxidative C–O coupling **3j** was obtained in 83% yield with the use of 2 equiv. of SiO_2 (entry 2), while in the absence of silica gel compound **3j** was formed in trace or low yield (entries 1 and 3). The mixture of products **3j** and **4j** with the predominance of **3j** was prepared upon raising the temperature from 25 to 100 °C (entries 4–6). At the temperature of 120 °C (entry 7) and 200 °C (entry 9), only decarboxylation product **4j** was isolated. Note that experiment at 120 °C without



	R^1	R^2	R^3
1a	Me	$(CH_2)_2C(O)OEt$	Me
1b	Me	CH_2Ph	Me
1c	Me	4-$ClC_6H_4CH_2$	Me
1d		$(CH_2)_3$	Me
1e		$(CH_2)_4$	Me
1f	Me	$(CH_2)_2C(O)Me$	Me
1g	Me	Me	OEt
1h	Me	Bu	OEt
1i	Me	$(CH_2)_2CN$	OEt
1j	Me	CH_2Ph	OEt
1k		$(CH_2)_3$	OEt
1l		$(CH_2)_4$	OEt
1m		$O(CH_2)_2$	OEt

2a R^4 = Et
2b R^4 = Bu
2c $R^4 + R^4 = (CH_2)_3$
2d $R^4 + R^4 = (CH_2)_4$

Reactants	Product	Yield (%)
1a + **2a**	**4a**	82
1b + **2a**	**4b**	79
1c + **2a**	**4c**	78
1d + **2a**	**4d**	85
1e + **2a**	**4e**	87
1f + **2a**	**4f**	69
1g + **2a**	**4g**	86
1h + **2a**	**4h**	79
1i + **2a**	**4i**	61
1j + **2a**	**4j**	87
1k + **2a**	**4k**	81
1l + **2a**	**4l**	89
1m + **2a**	**4m**	46
1k + **2b**	**4n**	59
1j + **2c**	**4o**	36
1l + **2c**	**4p**	38
1b + **2d**	**4q**	36
1j + **2d**	**4r**	47
1l + **2d**	**4s**	51

Scheme 1 *Reagents and conditions*: **1** (1 equiv.), SiO_2 (2 equiv.), **2** (1.5 equiv.), 120 °C, 2 h.

Table 1 Optimization of SiO_2-mediated decarboxylation of tetracarbonyl compound **3j** prepared *in situ* from β-oxo ester **1j** and malonyl peroxide **2a**.[a]

Entry	Molar ratio SiO_2 : **1j**	*T*/°C	*t*/h	Conversion of **1j** (%)	Isolated yield of **3j** (%)	Isolated yield of **4j** (%)
1	no SiO_2	25	24	<10	trace	–
2	2:1	25	24	89	83	trace
3	no SiO_2	40	24	49	37	–
4	2:1	70	2	>95	68	19
5	2:1	70	9	>95	66	24
6	2:1	100	2	>95	58	29
7	2:1	120	2	>95	–	87
8	no SiO_2	120	2	>95	27	49
9	2:1	200	2	>95	–	85

[a] Reaction conditions: β-oxo ester **1j** (100.0 mg, 0.45 mmol, 1.0 equiv.) was mixed with SiO_2 (54.4 mg, 0.9 mmol, 2.0 equiv.); then malonyl peroxide **2a** (107.6 mg, 0.68 mmol, 1.5 equiv.) was slowly loaded into well-stirred reaction mixture within 5 min; the reaction mass was stirred from 2 to 24 h at 25–200 °C.

SiO_2 (entry 8) resulted in the mixture of **3j** and **4j**. The use of silica gel makes it possible to avoid heating to 200 °C, which enters the temperature range of the critical stability for the majority of multifunctional organic compounds.

The additional experiments were performed to prove the consistent reaction pathway: oxidation of the starting substrate **1** to give the C–O coupling product **3** and its following conversion into compound **4**. The C–O coupling products **3a**, **3h** and **3j** were heated with silica gel for 2 h to afford the corresponding decarboxylation products **4a** (73%), **4h** (69%) and **4j** (87%). Note that malonyl peroxides in all experiments should be slowly added for 5 min to avoid strong thermal effects. The investigation of the silica gel by field emission scanning electron microscopy revealed that it consisted of particles with size about 100 μm (Figure S1, see Online Supplementary Materials). The morphology of the silica gel surface was irregular. The energy dispersive X-ray microanalysis (EDX) showed that used silica gel did not contain impurities of heavy metals (Figure S2).

Under the optimal conditions of one-pot C–O coupling/decarboxylation (Table 1, entry 7) the straightforward synthesis of C–O coupling/decarboxylation products **4a**–**s** from polycarbonyl compounds **1** and malonyl peroxides **2** was performed.[†]

Based on the results of the synthesis of structurally different decarboxylation products **4a**–**l**, in 61–89% yields, it could be expected that the above-described method for C–O coupling/decarboxylation can be extended to a broad scope of di- and tricarbonyl compounds. The product **4m** of the C–O coupling of keto lactone **1m** with diethylmalonyl peroxide **2a** was prepared in moderate 46% yield. When dibutylmalonyl peroxide **2b** and dicarbonyl compound **1k** were used, decarboxylation product **4n** was formed in 59% yield. Among C–O coupling products **4o**–**s** with cyclic malonyl peroxides **2c**,**d**, the best yields were achieved in case of cyclopentane malonyl peroxide **2d**.

Thus, silica gel was found to be highly active catalyst for decarboxylation of tetracarbonyl compounds leading to tricarbonyl compounds under heterogeneous conditions without a solvent. For the first time standard silica gel was applied for selective decarboxylation without deeper oxidative transformations. Silica gel most effectively acts as a mediator of C–O coupling and further decarboxylation at the temperature of 120 °C, which allows one to avoid overheating of the reaction mass.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.017.

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[†] *Caution*! Although malonyl peroxides possess sufficient thermostability, safety precautions should be applied.

General procedure. β-Diketone **1a**–**f** (500.0 mg, 2.23–3.96 mmol, 1.0 equiv.) or β-oxoester **1g**–**l** (500.0 mg, 2.27–3.47 mmol, 1.0 equiv.) or lactone **1m** (500.0 mg, 3.90 mmol, 1.0 equiv.) was mixed with SiO_2 (267.0–475.6 mg, 4.45–7.93 mmol, 2.0 equiv.). Then malonyl peroxide **2** (505.7–1028.8 mg, 3.34–5.95 mmol, 1.5 equiv.) was slowly loaded into the well-stirred reaction mixture within 5 min. The reaction mass was stirred at 120 °C for 2 h. Silica gel (0.060–0.200 mm, 60 Å, CAS 7631-86-9) was used in all reactions.

Ethyl 2-benzyl-2-(2-ethylbutanoyloxy)-3-oxobutanoate **4j**. Yield 658 mg (1.97 mmol, 87%). Colourless oil, R_f = 0.40 [eluent: light petroleum (40–70)–EtOAc (5:1) with 2% AcOH]. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C) δ: 0.92–0.97 (m, 6H), 1.18 (t, 3H, *J* 7.3 Hz), 1.50–1.77 (m, 4H), 2.12–2.36 (m, 4H), 3.46 (d, 1H, CH_2, *J* 13.9 Hz), 3.54 (d, 1H, CH_2, *J* 13.9 Hz), 4.16 (q, 2H, *J* 7.3 Hz), 7.11–7.14 (m, 2H), 7.23–7.28 (m, 3H). ^{13}C NMR (75.48 MHz, $CDCl_3$, 25 °C) δ: 11.5, 11.7, 13.8, 24.3, 24.6, 27.8, 39.7, 48.2, 62.1, 87.6, 127.3, 128.2, 130.1, 134.1, 166.9, 174.7, 202.2. HRMS (ESI), *m*/*z*: 357.1667 $[M+Na]^+$ (calc. for $[C_{19}H_{26}NaO_5]^+$, *m*/*z*: 357.1672). Found (%): C, 68.43; H, 7.75. Calc. for $C_{19}H_{26}O_5$ (%): C, 68.24; H, 7.84.