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Reductive Knoevenagel Condensation with the Zn–AcOH System

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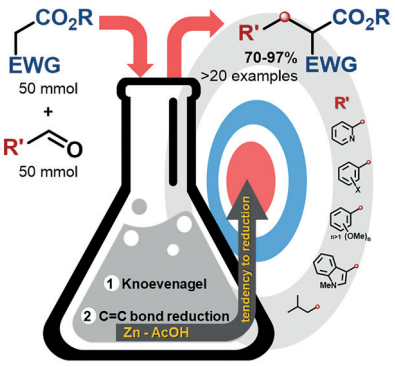


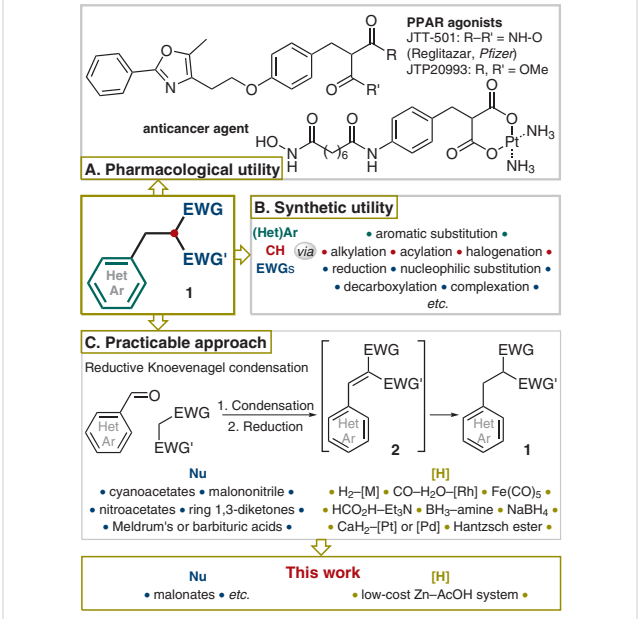
Received: 21.05.2020
Accepted after revision: 16.09.2020
Published online: 29.10.2020
DOI: 10.1055/s-0040-1705940; Art ID: ss-2020-t0283-op

Abstract An efficient gram-scale one-pot approach to 2-substituted malonates and related structures is developed, starting from commercially available aldehydes and active methylene compounds. The technique combines Knoevenagel condensation with the reduction of the C=C bond in the resulting activated alkenes with the Zn–AcOH system. The relative ease with which the C=C bond reduction occurs can be traced to the accepting abilities of the substituents in the intermediate arylidene malonates.

Key words electron transfer, malonate, reduction, reductive alkylation, zinc

(Het)arylmethylmalonates **1** as well as their analogues with other electron-withdrawing groups (EWGs, i.e., COR, $CONR_2$, CN, etc.) attract significant interest in the context of their pharmacological and synthetic utility. Among 1,3-dicarbonyl derivatives **1**, dual PPAR agonists with antihyperglycemic and antihyperlipidemic activities [e.g., JTT-501 (Reglitazar), JTP20993 and their structural analogues][1] as well as anticancer agents[2] have been reported (Scheme 1A). The synthetic utility of compounds **1** is associated with possible modifications of the pronucleophilic CH acidic center, the aromatic ring, and EWGs (Scheme 1B).

Among the primary synthetic approaches to compounds **1**, the sequence that involves Knoevenagel condensation between aldehydes and active methylene compounds followed by the reduction of the newly formed C=C bond in alkenes **2** can be called essential (Scheme 1C). This technique is a valuable alternative to direct alkylation of active methylene compounds if one considers the possibility of double alkylation as well as the frequently preferable availability of aldehydes as compared to the corresponding alkyl halides. Meanwhile, it is well known that the viability



Scheme 1 Concept of this work

of a multi-step synthesis can be significantly improved by its reorganization into a step-, time- and waste-economy one-pot protocol requiring no isolation of intermediates.[3]

The approach of simultaneous Knoevenagel condensation and reduction with an H_2–Pd/C system has been reported as early as 1944.[4] As of now, several protocols for reductive Knoevenagel condensation have been developed, employing different reducing agents: H_2 with noble metal-based catalysts (Rh,[5] Pd[6]); syngas–[Ru];[7] CO with noble-metal-based catalysts;[8] $Fe(CO)_5$;[9] HCO_2H–Et_3N;[10] BH_3–amine;[11] $NaBH_3CN$;[12] $NaBH_4$;[13] $NaTeH_4$;[14] CaH_2;[15] organic hydrides (Hantzsch ester, 2,3-dihydro-1*H*-benzimidazoles

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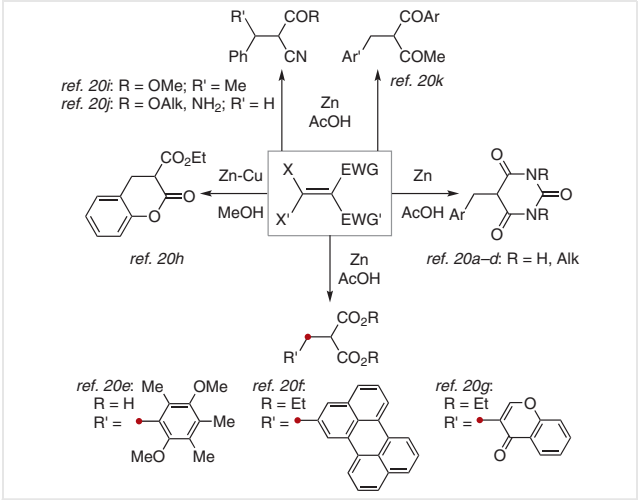
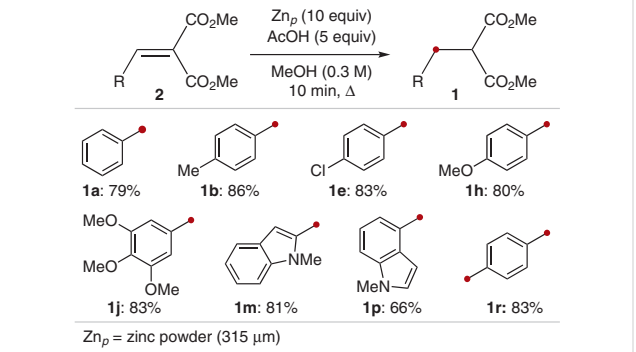
or 2-phenyl-2,3-dihydro-1,3-benzothiazole generated in situ);[16,17] and even HI formed in situ.[18] In almost all of these cases, very reactive substrates, such as cyanoacetates, malononitrile, nitroacetates, ring 1,3-diketones, Meldrum's or barbituric acid derivatives, were used as active methylene compounds. These can rapidly and efficiently afford intermediate products with high electron affinity. At the same time, malonate derivatives usually exhibit poor results in these tandem processes.[6a,f,8c,15,16a] Therefore, a bypass synthetic approach to malonates via Meldrum's acid derivatives was developed.[16b]

The ability of the Zn–H^+ systems to reduce electrophilic alkenes, particularly donor-acceptor substrates such as chalcone,[19] has been known since the 19th century. Since that time, Zn–H^+ systems were successfully used for hydrogenolysis of α,β-unsaturated compounds, including 1,3-dicarbonyl derivatives generally synthesized via Knoevenagel condensation (Scheme 2).[20] However, the use of this low-cost and convenient reducing agent in a one-pot reductive Knoevenagel condensation is restricted to a single example reported for highly reactive barbiturate derivatives.[20c] Herein, we describe an efficient technique for one-pot Knoevenagel condensation and C=C bond hydrogenolysis with the Zn–AcOH system, allowing for the introduction of poorly reactive malonates as well as other commonly used active methylene compounds.



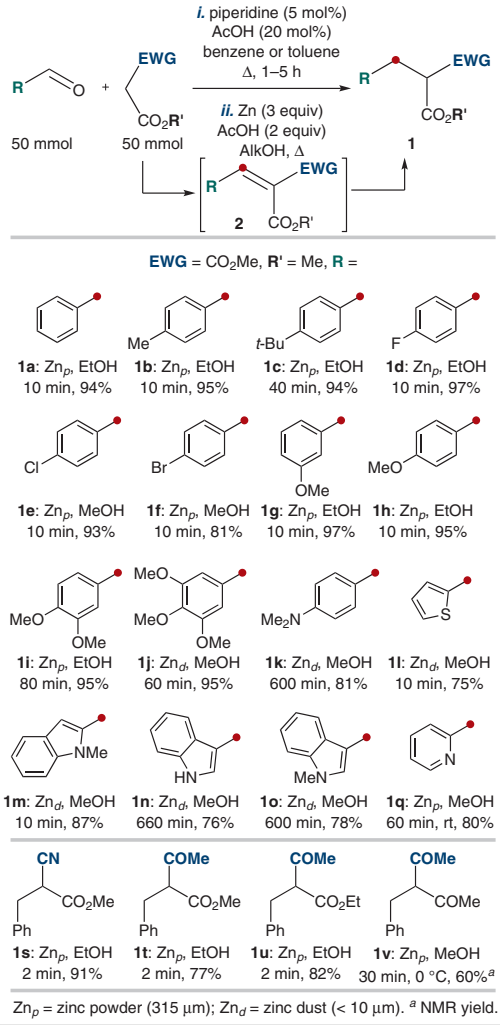
Scheme 2 Examples of 1,3-dicarbonyl derived-alkene hydrogenolysis with Zn–H^+ systems

Initially, we tested the isolated malonate derivatives **2** under conditions that were identical to those developed earlier in our group for donor-acceptor cyclopropane hydrogenolysis and reductive condensation of NO_2-substituted Knoevenagel alkenes, leading to quinoline derivatives (Scheme 3).[21] In the presence of 10 equivalents of Zn powder and 5 equivalents of AcOH, alkenes **2a**,**b**,**e**,**h**,**j**,**m**,**p**,**r** are completely converted into the corresponding alkanes **1** within 10 minutes in MeOH under reflux, regardless of the donating ability of a (het)aryl substituent in **2**.



Scheme 3 Hydrogenolysis of alkenes **2** with Zn–AcOH system

High concentration of reactants in the Knoevenagel step together with acidic conditions (1:4 piperidine/AcOH was used as a catalyst) provided an opportunity for combining this step with C=C bond hydrogenolysis in a protic medium. In our experience,[21a] even substoichiometric amounts of AcOH (0.5 equiv) are sufficient to carry out hydrogenolysis in AlkOH despite significant deceleration. Therefore, in the one-pot synthesis of **1**, we reduced the amounts of Zn and AcOH to 3 and 2 equivalents, respectively, while replacing MeOH with EtOH, with the aim of practicability (particularly toward gram-scale synthesis). This optimization immediately differentiated alkenes **2** with respect to their accepting abilities. We revealed that alkenes **2a**–**h** with phenyl, tolyl, mono-halogen-, and mono-alkoxyphenyl groups readily underwent hydrogenolysis in the presence of Zn powder in 10 minutes in EtOH under reflux (Scheme 4). However, to achieve complete reduction of dimethoxy derivative **2i**, prolonged heating was required along with additional amounts of AcOH. These conditions triggered transesterification. Therefore, for the highly donating 3,4,5-trimethoxy and 4-dimethylamino derivatives **2j**,**k**, Zn dust (<10 μm) was used instead of Zn powder (315 μm). However, this made the isolation of **2** somewhat complicated. The significant increase in the reaction time (**2j**: 1 h, **2k**: 10 h) and the use of MeOH as a solvent once again allowed to synthesize **1j**,**k** chemoselectively and in high yields. The use of 4-nitrobenzaldehyde in the studied process is complicated by the involvement of the NO_2 group. The treatment of the corresponding alkene **2**, dimethyl (4-nitrobenzylidene)malonate, with Zn–AcOH resulted in rapid NO_2-into-NH_2 reduction. However, further reduction proceeded ambiguously accompanied by side processes, including retro-Knoevenagel condensation (that is typical for compounds with electron-abundant groups)[22] and irreversible conversion of the regenerated aldehyde into an alcohol.

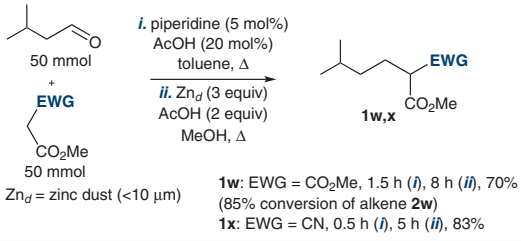


Scheme 4 One-pot Knoevenagel condensation and C=C bond reduction starting from (het)aryl aldehydes

The impact of the electronic nature of substituent R in **2** on the rate of hydrogenolysis was observed more palpably for heteroaryl-substituted alkenes **2l**–**o**,**q**. Alkene **2l**, containing the phenyl-like 2-thienyl group, as well as 2-indolyl-substituted alkene **2m**, were easily converted into alkanes **1l**,**m** within 10 minutes in MeOH under reflux. However, for **2n**,**o** with the 3-indolyl substituents of a more donating nature, complete conversion to **1n**,**o** could only be achieved in 10–11 hours. Oppositely, 2-pyridyl-substituted alkene **2q** underwent very easy reduction at room temperature with Zn powder.

Next, we studied cyanoacetate, acetoacetates, and acetylacetone in this one-pot process (Scheme 4). The hydrogenolysis of cyano and keto esters **2s**–**u** proceeded more intensively versus malonates, leading to **1s**–**u** in high yields within 2 minutes. Diketo derivative **2v** was found to possess the highest reactivity within the studied series of compounds. The hydrogenolysis of **2v** proceeded at 0 °C in 30 minutes with low chemoselectivity. The NMR yield of the target alkane **1v** only amounted to 60%, whereas the unidentified side products were found to be inseparable by means of column chromatography. Among the possible competitive processes prohibiting chemoselectivity, the Clemmensen-like reduction of a keto group as well as the radical dimerization of conjugated ketones of the **2v** type can be singled out.[19b]

The application of the developed one-pot process for aliphatic aldehydes is less viable since in this case direct alkylation of active methylene compounds is more relevant due to frequent availability of the corresponding alkyl halides. However, in order to demonstrate the applicability of our one-pot protocol for aliphatic aldehydes, we used isovaleraldehyde in reactions with dimethyl malonate and methyl cyanoacetate (Scheme 5). The Knoevenagel steps were completed in 1.5 hours (**2w**) and 0.5 hour (**2x**). The rate of hydrogenolysis of alkyl-substituted methylidenemalonate **2w** with the Zn–AcOH system was comparable with that for arylidenemalonates with donor (het)aryl substituents (e.g., **2k**,**n**,**o**). 85% conversion of **2w** into **1w** was achieved in 8 hours. As one should expect, cyanoester **2x** exhibited higher reactivity versus malonate **2x**.



Scheme 5 One-pot protocol with isovaleraldehyde

In conclusion, we have developed a convenient one-pot synthesis of 2-substituted malonates and their cyano- and keto-analogues via reductive Knoevenagel condensation from the commonly available aldehydes and active methylene compounds with Zn–AcOH as a low-cost reductive system. The developed protocol allows for the involvement of malonate derivatives that usually exhibit low reactivity in similar processes with other reducing agents. However, the highly reactive 1,3-diketones demonstrate low chemoselectivity in this approach. The tendency of intermediate arylidenemalonates to undergo hydrogenolysis correlates to the electronic nature of (het)aryl substituents conjugated with the C=C bond.

Reagents were purchased from commercial sources and used without further purification. NMR spectra were acquired either on Bruker Avance 400 MHz or on Bruker Avance 600 MHz spectrometers at r.t.; the chemical shifts δ were measured in ppm with respect to solvent (^{1}H: $CDCl_3$, δ = 7.27; ^{13}C: $CDCl_3$, δ = 77.0). Standard abbreviations are used to designate the splitting patterns. Coupling constants (*J*) are

given in hertz (Hz). The structures of compounds were elucidated with the aid of 1D NMR (^{1}H, ^{13}C{^{1}H}, ^{13}C off-resonace decoupling). High-resolution and accurate mass measurements were carried out using a Bruker microTOF-Q ESI-TOF (Electro Spray Ionization/Time of Flight) and Thermo Scientific LTQ Orbitrap mass spectrometers. Melting points were determined using Electrothermal IA 9100 capillary melting point apparatus. Analytical TLC was carried out with silica gel plates (silica gel 60, F_{254}, supported on aluminum foil) visualized with UV lamp (254 nm). Column chromatography was performed on silica gel 60 (230–400 mesh). Zn powder (315 μm) and Zn dust (<10 μm) are commercial products. Spectral data for compounds **1a**,**b**,**d**–**j**,**m**–**o**,**s**–**u**,**x** are consistent with those reported previously.

Hydrogenolysis of Knoevenagel Alkenes 2 with the Zn–AcOH System;[21a] General Procedure 1 (GP1)

To a solution of the corresponding alkene **2** (1 equiv) in MeOH (0.3 M) were added Zn powder (10 equiv) and AcOH (5 equiv) sequentially. The reaction mixture was stirred under reflux for 10 min. The resulting suspension was cooled and then the remaining metallic Zn was filtered off using EtOAc for washing. The combined organic fractions were concentrated under reduced pressure. The residue was mixed up with brine and extracted with EtOAc. The combined organic fractions were washed once with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EtOAc; or PE/Et_2O).

One-Pot (OP) Reductive Knoevenagel Condensation with the Zn–AcOH System; General Procedure 2 (GP2)

Caution! Although we did not experience any problems with the studied reactions, Zn dust is potentially flammable material. Its reactions with acids are highly exothermic with releasing flammable H_2 gas. Safety precautions are required.

A mixture of the corresponding aldehyde (50 mmol), active methylene compound (50 mmol), piperidine (0.25 mL, 2.5 mmol), and AcOH (0.58 mL, 10 mmol) in benzene (or toluene, if noticed, 40 mL) was heated under reflux with a 20 mL Dean–Stark trap for 1–5 h (until ca. 1 mL of H_2O was collected). The reaction mixture was allowed to cool down to r.t. Then it was diluted with the corresponding alcohol (50 mL) (Scheme 4), followed by the addition of Zn metal in either powdered or dust form (9.8 g, 0.15 mol) and AcOH (5.8 mL, 0.10 mol). In the case of cyano and keto derivatives, AcOH was added dropwise within 5 min under vigorous stirring. The reaction mixture was stirred under conditions specified (Schemes 4 and 5). The resulting suspension was cooled, if needed, and then the remaining Zn metal was filtered off using EtOAc for washing (Büchner funnel was used in the case of Zn dust). The combined organic fractions were concentrated under reduced pressure. The residue was mixed up with brine (50 mL) and extracted with EtOAc (2 × 120 mL). The combined organic fractions were washed once with H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EtOAc, or CH_2Cl_2).

Dimethyl 2-Benzylmalonate (1a)[15,16b,23a]

Yield: 10.41 g (94%, GP2: benzene), 10.09 g (91%, GP2: toluene), 2.45 g (79% for 14 mmol run, GP1); colorless oil; R_f = 0.48 (PE/Et_2O 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.24 (br d, ^3J = 7.7 Hz, 2 H, CH_2), 3.70 (t, ^3J = 7.7 Hz, 1 H, CH), 3.70 (s, 6 H, 2 × CH_3O), 7.19–7.25 (m, 3 H, C_6H_5), 7.27–7.31 (m, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 34.6 ($^1J_{CH}$ = 132 Hz, CH_2), 52.4 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 53.5 ($^1J_{CH}$ = 134 Hz, CH), 126.7 (CH, C_6H_5), 128.4 (2 × CH, C_6H_5), 128.6 (2 × CH, C_6H_5), 137.6 (C, C_6H_5), 169.1 (2 × CO_2Me).

Dimethyl 2-(4-Methylbenzyl)malonate (1b)[23a]

Yield: 11.25 g (95%, GP2), 4.45 g (86% for 22 mmol run, GP1); colorless oil; R_f = 0.83 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.32 (s, 3 H, CH_3), 3.20 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.67 (t, ^3J = 7.8 Hz, 1 H, CH), 3.71 (s, 6 H, 2 × CH_3O), 7.09 (br s, 4 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 20.9 ($^1J_{CH}$ = 126 Hz, CH_3), 34.3 ($^1J_{CH}$ = 132 Hz, CH_2), 52.4 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 53.6 ($^1J_{CH}$ = 134 Hz, CH), 128.5 (2 × CH, Ar), 129.1 (2 × CH, Ar), 134.5 (C, Ar), 136.2 (C, Ar), 169.1 (2 × CO_2Me).

Dimethyl (4-*tert*-Butylbenzyl)malonate (1c)

Yield: 13.07 g (94%, GP2); yellowish oil; R_f = 0.86 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.31 (s, 9 H, 3 × CH_3), 3.21 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.69 (t, ^3J = 7.8 Hz, 1 H, CH), 3.72 (s, 6 H, 2 × CH_3O), 7.12–7.15 (m, 2 H, Ar), 7.30–7.33 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 31.3 (3 × CH_3), 34.2 (CH_2), 34.3 (C), 52.5 (2 × CH_3O), 53.5 (CH), 125.4 (2 × CH, Ar), 128.3 (2 × CH, Ar), 134.6 (C, Ar), 149.5 (C, Ar), 169.3 (2 × CO_2Me).

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{16}H_{21}O_4^-$: 277.1445; found: 277.1447.

Dimethyl 2-(4-Fluorobenzyl)malonate (1d)[23b]

Yield: 11.63 g (97%, GP2); yellowish oil; R_f = 0.78 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.18 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.63 (t, ^3J = 7.8 Hz, 1 H, CH), 3.68 (s, 6 H, 2 × CH_3O), 6.95 (dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HF}$ = 8.6 Hz, 2 H, Ar), 7.15 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HF}$ = 5.3 Hz, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 33.8 (CH_2), 52.5 (2 × CH_3O), 53.5 (CH), 115.3 ($^2J_{CF}$ = 21 Hz, 2 × CH), 130.2 ($^3J_{CF}$ = 8 Hz, 2 × CH), 133.3 ($^4J_{CF}$ = 3 Hz, C), 161.7 ($^1J_{CF}$ = 245 Hz, C), 169.0 (2 × CO_2Me).

Dimethyl 2-(4-Chlorobenzyl)malonate (1e)[23a]

Yield: 11.94 g (93%, GP2), 2.15 g (83% for 10 mmol run, GP1); yellowish oil; R_f = 0.50 (PE/Et_2O 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.19 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.64 (t, ^3J = 7.8 Hz, 1 H, CH), 3.71 (s, 6 H, 2 × CH_3O), 7.14 (d, ^3J = 8.3 Hz, 2 H, Ar), 7.25 (d, ^3J = 8.3 Hz, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 34.0 ($^1J_{CH}$ = 132 Hz, CH_2), 52.6 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 53.4 ($^1J_{CH}$ = 134 Hz, CH), 128.7 (2 × CH, Ar), 130.2 (2 × CH, Ar), 132.7 (C, Ar), 136.2 (C, Ar), 169.0 (2 × CO_2Me).

Dimethyl 2-(4-Bromobenzyl)malonate (1f)[23c]

Yield: 12.16 g (81%, GP2); yellowish oil; R_f = 0.54 (PE/Et_2O 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.15 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.62 (t, ^3J = 7.8 Hz, 1 H, CH), 3.67 (s, 6 H, 2 × CH_3O), 7.06 (d, ^3J = 8.5 Hz, 2 H, Ar), 7.37 (d, ^3J = 8.5 Hz, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 33.9 ($^1J_{CH}$ = 132 Hz, CH_2), 52.5 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 53.1 ($^1J_{CH}$ = 134 Hz, CH), 120.6 (C, Ar), 130.4 (2 × CH, Ar), 131.5 (2 × CH, Ar), 136.6 (C, Ar), 168.8 (2 × CO_2Me).

Dimethyl 2-(3-Methoxybenzyl)malonate (1g)[23a]

Yield: 12.29 g (97%, GP2); colorless oil; R_f = 0.71 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.21 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.68 (t, ^3J = 7.8 Hz, 1 H, CH), 3.71 (s, 6 H, 2 × CH_3O), 3.79 (s, 3 H, CH_3O), 6.74–6.79 (m, 2 H, Ar), 7.18–7.21 (m, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 34.7 ($^1J_{CH}$ = 131 Hz, CH_2), 52.5 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 53.5 ($^1J_{CH}$ = 134 Hz, CH), 55.1 ($^1J_{CH}$ = 144 Hz, CH_3O), 112.2 (CH, Ar), 114.4 (CH, Ar), 121.0 (CH, Ar), 129.5 (CH, Ar), 139.3 (C, Ar), 159.7 (C, Ar), 169.2 (2 × CO_2Me).

Dimethyl 2-(4-Methoxybenzyl)malonate (1h)[15,23a]

Yield: 11.96 g (95%, GP2), 2.61 g (80% for 13 mmol); colorless oil; R_f = 0.39 (PE/Et_2O 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.15 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.62 (t, ^3J = 7.8 Hz, 1 H, CH), 3.67 (s, 6 H, 2 × CH_3O), 3.74 (s, 3 H, CH_3O), 6.79 (d, ^3J = 8.8 Hz, 2 H, Ar), 7.09 (d, ^3J = 8.8 Hz, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 33.8 ($^1J_{CH}$ = 132 Hz, CH_2), 52.3 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 53.6 ($^1J_{CH}$ = 134 Hz, CH), 54.9 ($^1J_{CH}$ = 144 Hz, CH_3O), 113.7 (2 × CH, Ar), 129.5 (C, Ar), 129.6 (2 × CH, Ar), 158.3 (C, Ar), 169.0 (2 × CO_2Me).

Dimethyl 2-(3,4-Dimethoxybenzyl)malonate (1i)[23d]

Yield: 13.40 g (95%, GP2); yellowish oil; R_f = 0.52 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.15 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.64 (t, ^3J = 7.8 Hz, 1 H, CH), 3.69 (s, 6 H, 2 × CH_3O), 3.83 (s, 3 H, CH_3O), 3.84 (s, 3 H, CH_3O), 6.71 (br d, ^4J = 2.0 Hz, 1 H, Ar), 6.72 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1 H, Ar), 6.76 (br d, ^3J = 8.0 Hz, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 34.3 (CH_2), 52.4 (2 × CH_3O), 53.7 (CH), 55.69 (CH_3O), 55.71 (CH_3O), 111.1 (CH, Ar), 111.9 (CH, Ar), 120.7 (CH, Ar), 130.1 (C, Ar), 147.7 (C, Ar), 148.7 (C, Ar), 169.1 (2 × CO_2Me).

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_{17}O_6^-$: 281.1031; found: 281.1031.

Dimethyl 2-(3,4,5-Trimethoxybenzyl)malonate (1j)[23e]

Yield: 14.78 g (95%, GP2), 2.82 g (83% for 11 mmol run, GP1); colorless solid; mp 75–76 °C; R_f = 0.29 (PE/Et_2O 1:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.13 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.63 (t, ^3J = 7.8 Hz, 1 H, CH), 3.68 (s, 6 H, 2 × CH_3O), 3.77 (s, 3 H, CH_3O), 3.79 (s, 6 H, 2 × CH_3O), 6.38 (s, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 34.9 ($^1J_{CH}$ = 132 Hz, CH_2), 52.4 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 53.5 ($^1J_{CH}$ = 134 Hz, CH), 55.9 ($^1J_{CH}$ = 144 Hz, 2 × CH_3O), 60.6 ($^1J_{CH}$ = 144 Hz, CH_3O), 105.6 (2 × CH, Ar), 133.3 (C, Ar), 136.7 (C, Ar), 153.0 (2 C, Ar), 169.0 (2 × CO_2Me).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}O_7Na^+$: 335.1101; found: 335.1098.

Dimethyl [4-(Dimethylamino)benzyl]malonate (1k)

Yield: 10.76 g (81%, GP2); yellow oil; R_f = 0.72 (PE/EtOAc 1:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.92 [s, 6 H, $(CH_3)_2$N], 3.15 (br d, ^3J = 7.8 Hz, 2 H, CH_2), 3.64 (t, ^3J = 7.8 Hz, 1 H, CH), 3.71 (s, 6 H, 2 × CH_3O), 6.85–6.88 (m, 2 H, Ar), 7.06–7.09 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 33.8 ($^1J_{CH}$ = 132 Hz, CH_2), 40.5 [$^1J_{CH}$ = 135 Hz, $(CH_3)_2$N], 52.3 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 53.9 ($^1J_{CH}$ = 134 Hz, CH), 112.7 (2 × CH, Ar), 125.4 (C, Ar), 129.3 (2 × CH, Ar), 149.4 (C, Ar), 169.3 (2 × CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_4^+$: 266.1387; found: 266.1389.

Dimethyl (Thiophen-2-ylmethyl)malonate (1l)

Yield: 8.53 g (75%, GP2); yellowish oil; R_f = 0.70 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.44 (br d, ^3J = 7.7 Hz, 2 H, CH_2), 3.70 (t, ^3J = 7.7 Hz, 1 H, CH), 3.72 (s, 6 H, 2 × CH_3O), 6.82–6.84 (m, 1 H, Th), 6.89 (dd, ^3J = 5.2 Hz, ^3J = 3.4 Hz, 1 H, Th), 7.13 (dd, ^3J = 5.2 Hz, ^4J = 1.2 Hz, 1 H, Th).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 28.8 ($^1J_{CH}$ = 133 Hz, CH_2), 52.5 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 53.8 ($^1J_{CH}$ = 134 Hz, CH), 124.2 (CH, Th), 125.9 (CH, Th), 126.8 (CH, Th), 139.7 (C, Th), 168.6 (2 × CO_2Me).

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{10}H_{11}O_4S^-$: 227.0384; found: 227.0381.

Dimethyl [(1-Methyl-1*H*-indol-2-yl)methyl]malonate (1m)[23f,g]

Yield: 11.98 g (87%, GP2), 0.82 g (81% for 3.7 mmol run, GP1); yellow solid; mp 83–84 °C (Lit.[8] mp 87–89 °C); R_f = 0.32 (PE/Et_2O 2:1). For column chromatography, CH_2Cl_2 was used as an eluent.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.42 (d, ^3J = 7.7 Hz, 2 H, CH_2), 3.72 (s, 3 H, CH_3N), 3.77 (s, 6 H, 2 × CH_3O), 3.90 (t, ^3J = 7.7 Hz, 1 H, CH), 6.26 (br s, 1 H, Ind), 7.07–7.12 (m, 1 H, Ind), 7.18–7.23 (m, 1 H, Ind), 7.30 (br d, ^3J = 8.2 Hz, 1 H, Ind), 7.55 (br d, ^3J = 7.9 Hz, 1 H, Ind).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.9 (CH_2), 29.5 (CH_3N), 51.0 (CH), 52.8 (2 × CH_3O), 99.5 (CH, Ind), 108.9 (CH, Ind), 119.4 (CH, Ind), 120.1 (CH, Ind), 121.1 (CH, Ind), 127.6 (C, Ind), 136.5 (C, Ind), 137.4 (C, Ind), 169.0 (2 × CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}NO_4^+$: 276.1230; found: 276.1231.

Dimethyl (1*H*-Indol-3-ylmethyl)malonate (1n)[23g,h]

Yield: 9.91 g (76%, GP2); brown oil; R_f = 0.50 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.48 (br d, ^3J = 7.7 Hz, 2 H, CH_2), 3.74 (s, 6 H, 2 × CH_3O), 3.90 (t, ^3J = 7.7 Hz, 1 H, CH), 7.02–7.03 (m, 1 H, Ind), 7.17–7.20 (m, 1 H, Ind), 7.22–7.26 (m, 1 H, Ind), 7.34–7.36 (m, 1 H, Ind), 7.65–7.67 (m, 1 H, Ind), 8.32 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 24.6 ($^1J_{CH}$ = 131 Hz, CH_2), 52.4 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 52.7 ($^1J_{CH}$ = 134 Hz, CH), 111.2 (CH, Ind), 111.6 (C, Ind), 118.3 (CH, Ind), 119.3 (CH, Ind), 121.9 (CH, Ind), 122.6 (CH, Ind), 126.8 (C, Ind), 136.1 (C, Ind), 169.7 (2 × CO_2Me).

Dimethyl [(1-Methyl-1*H*-indol-3-yl)methyl]malonate (1o)[23i]

Yield: 10.68 g (78%, GP2); brown solid; mp 78–79 °C; R_f = 0.59 (PE/EtOAc 2:1). For column chromatography, CH_2Cl_2 was used as an eluent.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.39–3.41 (m, 2 H, CH_2), 3.72 (s, 6 H, 2 × CH_3O), 3.74 (s, 3 H, CH_3N), 3.80 (t, ^3J = 7.6 Hz, 1 H, CH), 6.91 (br s, 1 H, Ind), 7.12–7.15 (m, 1 H, Ind), 7.22–7.25 (m, 1 H, Ind), 7.28–7.30 (m, 1 H, Ind), 7.59–7.61 (m, 1 H, Ind).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 24.5 ($^1J_{CH}$ = 132 Hz, CH_2), 32.5 ($^1J_{CH}$ = 138 Hz, CH_3N), 52.4 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 52.8 ($^1J_{CH}$ = 134 Hz, CH), 109.2 (CH, Ind), 110.3 (C, Ind), 118.5 (CH, Ind), 118.8 (CH, Ind), 121.5 (CH, Ind), 127.2 (CH, Ind), 127.4 (C, Ind), 136.8 (C, Ind), 169.5 (2 × CO_2Me).

Dimethyl [(1-Methyl-1*H*-indol-4-yl)methyl]malonate (1p)

Yield: 1.03 g (66% for 5.7 mmol run, GP1); brown solid; mp 55–56 °C; R_f = 0.26 (PE/Et_2O 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.55 (br d, ^3J = 7.7 Hz, 2 H, CH_2), 3.71 (s, 6 H, 2 × CH_3O), 3.79 (s, 3 H, CH_3N), 3.92 (t, ^3J = 7.7 Hz, 1 H, CH), 6.55 (br d, ^3J = 3.0 Hz, 1 H, Ind), 6.96 (d, ^3J = 7.1 Hz, 1 H, Ind), 7.08 (d, ^3J = 3.0 Hz, 1 H, Ind), 7.16 (dd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, 1 H, Ind), 7.23 (d, ^3J = 8.1 Hz, 1 H, Ind).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 32.4 ($^1J_{CH}$ = 133 Hz, CH_2), 32.9 ($^1J_{CH}$ = 138 Hz, CH_3N), 52.4 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 52.6 ($^1J_{CH}$ = 134 Hz, CH), 98.8 (CH, Ind), 108.0 (CH, Ind), 119.3 (CH, Ind), 121.5 (CH, Ind), 127.6 (C, Ind), 128.6 (CH, Ind), 129.7 (C, Ind), 136.6 (C, Ind), 169.5 (2 × CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}NO_4^+$: 276.1230; found: 276.1239.

Dimethyl (Pyridin-2-ylmethyl)malonate (1q)

Yield: 8.98 g (80%, GP2); green oil; R_f = 0.58 (PE/EtOAc 1:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.35 (br d, ^3J = 7.6 Hz, 2 H, CH_2), 3.67 (s, 6 H, 2 × CH_3O), 4.10 (t, ^3J = 7.6 Hz, 1 H, CH), 7.04–7.08 (m, 1 H, Py), 7.13–7.15 (m, 1 H, Py), 7.51–7.55 (m, 1 H, Py), 8.43–8.45 (m, 1 H, Py).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.3 ($^1J_{CH}$ = 131 Hz, CH_2), 50.6 ($^1J_{CH}$ = 135 Hz, CH), 52.4 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 121.5 (CH, Py), 123.3 (CH, Py), 136.2 (CH, Py), 149.1 (CH, Py), 157.5 (C, Py), 169.4 (2 × CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NO_4^+$: 224.0917; found: 224.0918.

Tetramethyl 2,2′-(Benzene-1,4-diyldimethanediyl)malonate (1r)

Yield: 0.84 g (83% for 2.8 mmol run, GP1); colorless solid; mp 96–97 °C; R_f = 0.49 PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.19 (d, ^3J = 7.8 Hz, 4 H, 2 × CH_2), 3.65 (t, ^3J = 7.8 Hz, 2 H, 2 × CH), 3.70 (s, 12 H, 4 × CH_3O), 7.11 (s, 4 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 34.3 (2 × CH_2), 52.5 (4 × CH_3O), 53.5 (2 × CH), 129.0 (4 × CH, Ar), 136.2 (2 C, Ar), 169.2 (4 × CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}O_8^+$: 367.1387; found: 367.1377.

Methyl 2-Cyano-3-phenylpropanoate (1s)[15,23a]

Yield: 8.64 g (91%, GP2); yellowish oil; R_f = 0.72 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.20 (dd, ^2J = 13.9 Hz, ^3J = 8.5 Hz, 1 H, CH_2), 3.29 (dd, ^2J = 13.9 Hz, ^3J = 5.8 Hz, 1 H, CH_2), 3.76 (dd, ^3J = 8.5 Hz, ^3J = 5.8 Hz, 1 H, CH), 3.79 (s, 3 H, CH_3O), 7.27–7.33 (m, 3 H, C_6H_5), 7.34–7.38 (m, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 35.6 ($^1J_{CH}$ = 134 Hz, CH_2), 39.4 ($^1J_{CH}$ = 138 Hz, CH), 53.4 ($^1J_{CH}$ = 148 Hz, CH_3O), 115.9 (CN), 127.7 (CH, C_6H_5), 128.8 (2 × CH, C_6H_5), 128.9 (2 × CH, C_6H_5), 135.1 (C, C_6H_5), 165.9 (CO_2Me).

Methyl 2-Benzyl-3-oxobutanoate (1t)[23a]

Yield: 7.93 g (77%, GP2); yellow oil; R_f = 0.79 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.17 (s, 3 H, CH_3), 3.17 (br d, ^3J = 7.7 Hz, 2 H, CH_2), 3.67 (s, 3 H, CH_3O), 3.81 (t, ^3J = 7.7 Hz, 1 H, CH), 7.16–7.22 (m, 3 H, C_6H_5), 7.26–7.28 (m, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 29.5 (CH_3), 33.9 (CH_2), 52.3 (CH_3O), 60.9 (CH), 126.6 (CH, C_6H_5), 128.5 (2 × CH, C_6H_5), 128.6 (2 × CH, C_6H_5), 137.9 (C, C_6H_5), 169.4 (CO_2Me), 202.2 (COMe).

Ethyl 2-Benzyl-3-oxobutanoate (1u)[23j]

Yield: 9.02 g (82%, GP2); yellow oil; R_f = 0.85 (PE/EtOAc 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.19–1.22 (m, 3 H, CH_3), 2.19 (br s, 3 H, $COCH_3$), 3.16 (dd, ^2J = 14.2 Hz, ^3J = 7.9 Hz, 1 H, CH_2), 3.19 (dd, ^2J = 14.2 Hz, ^3J = 7.4 Hz, 1 H, CH_2), 3.79 (dd, ^3J = 7.9 Hz, ^3J = 7.4 Hz, 1 H, CH), 4.13–4.20 (m, 2 H, CH_2O), 7.16–7.22 (m, 3 H, C_6H_5), 7.26–7.29 (m, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 150 MHz): δ =13.9 ($^1J_{CH}$ = 127 Hz, CH_3), 29.4 ($^1J_{CH}$ = 128 Hz, $COCH_3$), 33.9 ($^1J_{CH}$ = 131 Hz, CH_2), 61.2 ($^1J_{CH}$ = 132 Hz, CH), 61.3 ($^1J_{CH}$ = 148 Hz, CH_2O), 126.6 (CH, C_6H_5), 128.5 (2 × CH, C_6H_5), 128.7 (2 × CH, C_6H_5), 138.1 (C, C_6H_5), 169.0 (CO_2Et), 202.3 (COMe).

Dimethyl 2-Isopentylmalonate (1w)

Yield: 5.98 g (70%, 85% conversion, GP2: toluene); colorless oil; R_f = 0.57 (PE/EtOAc 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.86 (d, ^3J = 6.6 Hz, 6 H, 2 × CH_3), 1.14–1.18 (m, 2 H, CH_2), 1.49–1.58 (m, 1 H, CH), 1.85–1.90 (m, 2 H, CH_2), 3.29 (t, ^3J = 7.6 Hz, 1 H, CH), 3.71 (s, 6 H, 2 × CH_3O).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 22.3 ($^1J_{CH}$ = 124 Hz, 2 × CH_3), 26.8 ($^1J_{CH}$ = 130 Hz, CH_2), 27.8 ($^1J_{CH}$ = 132 Hz, CH), 36.3 ($^1J_{CH}$ = 126 Hz, CH_2), 51.9 ($^1J_{CH}$ = 132 Hz, CH), 52.3 ($^1J_{CH}$ = 148 Hz, 2 × CH_3O), 169.9 (2 × CO_2Me).

Methyl 2-Cyano-5-methylhexanoate (1x)[8a]

Yield: 7.04 g (83%, GP2: toluene); yellowish oil; R_f = 0.52 (PE/EtOAc 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.92 (d, ^3J = 6.7 Hz, 3 H, CH_3), 0.93 (d, ^3J = 6.7 Hz, 3 H, CH_3), 1.34–1.44 (m, 2 H, CH_2), 1.58–1.65 (m, 1 H, CH), 1.91–2.01 (m, 2 H, CH_2), 3.49 (dd, ^3J = 8.0 Hz, ^3J = 6.0 Hz, 1 H, CH), 3.83 (s, 3 H, CH_3O).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 21.9 ($^1J_{CH}$ = 125 Hz, CH_3), 22.1 ($^1J_{CH}$ = 125 Hz, CH_3), 27.4 ($^1J_{CH}$ = 132 Hz, CH), 27.7 ($^1J_{CH}$ = 128 Hz, CH_2), 35.5 ($^1J_{CH}$ = 128 Hz, CH_2), 37.4 ($^1J_{CH}$ = 136 Hz, CH), 53.2 ($^1J_{CH}$ = 148 Hz, CH_3O), 116.3 (CN), 166.6 (CO_2Me).

Funding Information

Research was supported by the Russian Foundation for Basic Research, grant number 18-03-00549.

Acknowledgment

The NMR measurements were carried out at the Center for Magnetic Tomography and Spectroscopy, Faculty of Fundamental Medicine of Lomonosov Moscow State University.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1705940.

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