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Solvent-free Knoevenagel condensations and Michael additions in the solid state and in the melt with quantitative yield

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Abstract—Numerous Knoevenagel condensations of solid or liquid aromatic aldehydes are performed with four barbituric acids, Meldrum's acid, dimedone, cyanoacetamide, malodinitrile and methyl cyanoacetate in stoichiometric mixtures of the solids or of stoichiometric melts. The product yields are quantitative in 23 reported cases and the products do not require purifying workup. Therefore, these reactions are truly solvent-free, atom economic and sustainable and no wastes are produced. They are highly superior to less productive so-called 'solvent-free' techniques using solid supports and microwave irradiation that require solvents for removal of the support or reagents or side products. Similarly, the solution reactions generally requiring catalysts suffer from low yields and purifying workup. The new techniques provide numerous common electron-poor alkenes very easily. These are valuable building blocks for example in Michael additions. Also the latter can be quantitatively obtained in stoichiometric melts in the absence of any auxiliaries or microwave irradiation and this is demonstrated with stable and rearranging/cyclizing Michael adducts using dimedone. The quantitative yields are most easily obtained if the products are formed in the solid-state or if they crystallize directly from the melt at the reaction temperature.

1. Introduction

Knoevenagel condensations of aldehydes with active methylene compounds belong to the important olefin syntheses. They are usually base-,[1] (Lewis)acid-,[2] or surfactant-catalyzed[2a] and thus create much wastes. Recently, there was interest in so-called 'solvent-free'[3,4] Knoevenagel condensations on solid supports that were promoted by infrared[5] or microwave irradiation.[6] Unfortunately, the latter techniques require solvents for the extraction from the solid supports (sometimes also for the preparation of the initial adsorbates) and do not yield pure products so that further solvents are used for purifying workup. Even catalyst-free Knoevenagel reactions in water solvent could not reach quantitative yields.[7–9]

We checked the improvement that can be expected[10–12] if solvent, solid support and microwave are avoided, and report now on quantitative yields in various Knoevenagel condensations from stoichiometric mixtures of pure reactants without the necessity for use of solvents, for removal of catalysts, or solvent-consuming purifying workup. This endeavour succeeded in numerous cases if the reactions could be run as solid-state reactions or as melt reactions with direct crystallization at the reaction temperature. The same benefits are observed if Michael additions are similarly performed with the now easily available building blocks.

2. Results and discussion

2.1. Barbituric acids and solid aromatic aldehydes

The aldehydes **1a–d** and the barbituric acids **2** do not melt upon ball-milling of stoichiometric mixtures but provide the solid products **3a–d** quantitatively and in pure form. Therefore, no purifying workup is required in the absence of solid supports, microwave or catalyst or solvent and the reactions are thus truly solvent-free. The water of reaction does not interfere as it is taken up by the crystals **3** and does not significantly dissolve **3a–d**. It is simply removed by evaporation (Scheme 1).

These syntheses proceed well at the 2 mmol scale in a small vibrational ball-mill (Table 1), but the reactions **a–d** can also be performed with stoichiometric 200 g batches in a 2 L horizontal ball-mill as was executed with the large scale syntheses of **3b** (1 h, with water cooling at 14–20°C) and **3c** (1 h, without cooling at ≤50°C).

The chemical structure of **3a–d** was secured by the IR, ^{1}H and ^{13}C NMR data and by the comparison of the melting points with the values of the literature. Clearly, our solid-state syntheses of **3** are vastly superior to the previous

Keywords: cascade reactions; 1,3-dicarbonyl compounds; Knoevenagel condensation; melt reaction; Michael addition; quantitative yield; solid-state synthesis; waste-free.

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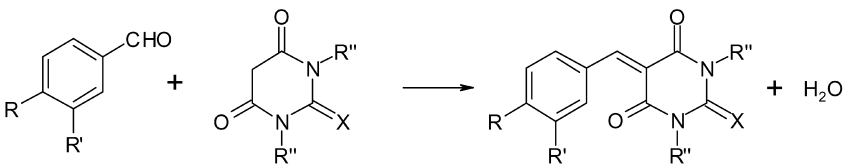


a: R=NMe_2, R'=H, R''= Et, X=S (r.t., 1 h)
b: R=OH, R'=H, R''= Me, X=O (r.t., 1 h)
c: R=OH, R'=H, R''= H, X=O (50°C, 1 h)
d: R=OH, R'=OMe, R''= H, X=O (50°C, 1 h)

Scheme 1. Quantitative un-catalysed Knoevenagel condensation of aromatic aldehydes with barbituric acids.

Table 1. Yields and melting points of products **3a–d** after ball-milling of **1** and **2**, and reference data

3	Reaction conditions	Yield (%)	Mp (°C)	Ref. mp (°C)	Conditions of Ref. reaction	Yield (%) in solution
a	1 h, rt	100	207–209	204–208[13]	EtOH, 20°C[13]	87[13]
b	1 h, rt	100	297	297–298 (HOAc)[14]	H_2O or EtOH (aq), steam bath[14]	generally 80–90[14]
c	1 h, rt to 50°C	100	299–301	>300 (EtOH)[15]	MeOH, rt, 12 h[16]	95[16]
d	1 h, 50°C	100	313	287–289[17]	EtOH[17]	Not reported

syntheses. They are waste-free when pure starting materials **1** and **2** are stoichiometrically applied.

2.2. Reactions of 1 with Meldrum's acid

The stoichiometric Knoevenagel reaction of **1a**,**b** with Meldrum's acid (**4**) at 50°C gave an intermediate melt from which **5a**,**b** crystallized quantitatively at the reaction temperature. These Knoevenagel condensations must therefore be termed as 'melt-reactions with direct crystallization' (Scheme 2).

As in the case of **3**, no removal of auxiliaries or purifying workup was required. The water of reaction was simply removed at 80°C in a vacuum and the reactions were waste-free if pure starting materials **1** and **4** were applied.

Previously, the compounds **5a**,**b** were obtained with only 81 and 80% yields in DMF.[18] The melting points fit and spectroscopic data support the chemical structure. Aromatic aldehydes condense to Meldrum's acid (**4**) also in water solution without catalyst but only with 60–95% yield.[9] Clearly, the use of the crystallization effects from the stoichiometric melt is largely superior to the previous techniques.

2.3. Reactions of 1 with dimedone

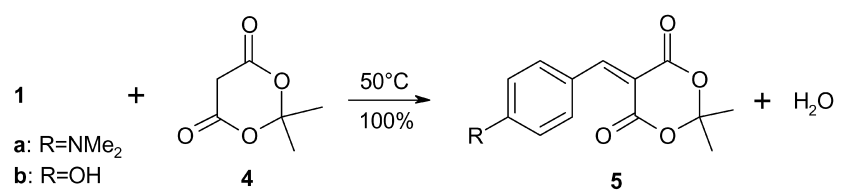
Dimedone (**6**) is not only a Knoevenagel reagent but it also adds easily to electron-poor alkenes in the Michael addition fashion. Thus, cascade reactions[12] of addition, elimination and addition could be achieved, but the intermediate alkenes were not available even in 1:1 experiments according to the present reaction conditions. The reaction cascades proceeded quantitatively from an intermediate melt with crystallization of **7b**,**e**,**f**,**g** at the reaction temperature. The water of reaction was removed at 80°C (in a vacuum) and unlike the solution reactions in DMF at 80°C (yields of 88, 80, 84, 90% respectively)[18] the auxiliary-free syntheses are highly superior as no wastes were produced. The structure **7** has two almost identical O–H···O hydrogen bridges (1.635 and 1.669 Å) according to B3LYP/6-31G* calculations with **7e**, and this tautomer in that conformation is the most stable that can be found (Scheme 3).

2.4. Reactions of 1 with cyanoacetamide

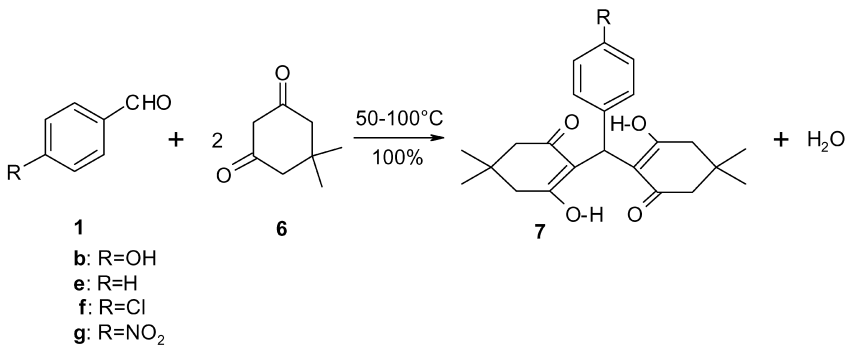
The Knoevenagel condensation of cyanoacetamide (**8**) with **1a**,**b**,**f** gave **9** in quantitative solid-state reactions and also in quantitative melt reactions (Table 2, Scheme 4).

The solid state reactions between **1** and **8** are too slow at room temperature and require a basic catalyst such as gaseous trimethylamine which can be easily removed together with the stoichiometric amount of the water of reaction to give a quantitative yield of pure **9a**,**b**,**f**. The catalyst (NMe_3) can be avoided if the temperature is raised up to 150–170°C for melt reactions with direct crystallization. The yields of **9a**,**b**,**f** were then also 100% (Table 2).

The (*E*)-configuration of **9** reflects the higher stability of these compounds that are apparently formed under thermodynamic control. The energy differences predicted by DFT (B3LYP/6-31G*) calculations between the (*E*)- and



Scheme 2. Quantitative syntheses of **5** in stoichiometric melts.



Scheme 3. Quantitative synthesis of **7**.

(*Z*)-isomers were 4.73, 4.90 and 4.89 kcal mol^{-1} for **9a**,**b**,**f**, respectively.

These syntheses of **9** are superior to the previous ones that did not provide the products in a pure form and thus created much wastes upon the purification procedures (Table 2).

2.5. Reactions of 1 with malodinitrile and methyl cyanoacetate

The reactions of the aldehydes **1b**,**e**,**f**,**g** with malodinitrile (**10**) or **1a**,**b** with methylcyanoacetate (**12**) to give **11** and **13** cannot be achieved in the solid-state at room temperature. However, the stoichiometric melt reactions without auxiliaries are quantitative and vastly superior to all previous syntheses of **11** and **13** that produced wastes by applying solvents, catalysts, or solid supports and/or microwave irradiation. Even the reaction in water without catalyst yielded the products **10b**,**e**,**f**,**g** only in yields of 84–98%.[8]

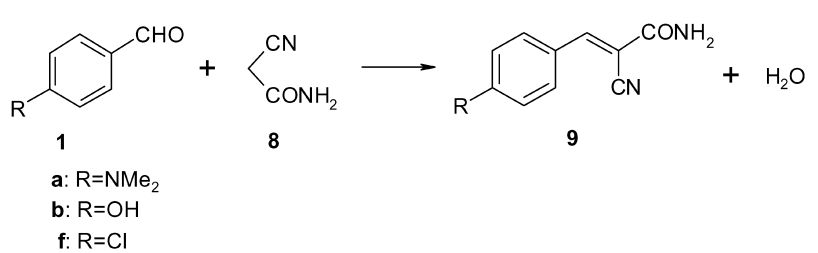
The compounds **11** and **13** are of importance as useful Michael addition acceptors (Scheme 5).

2.6. Michael additions with 11

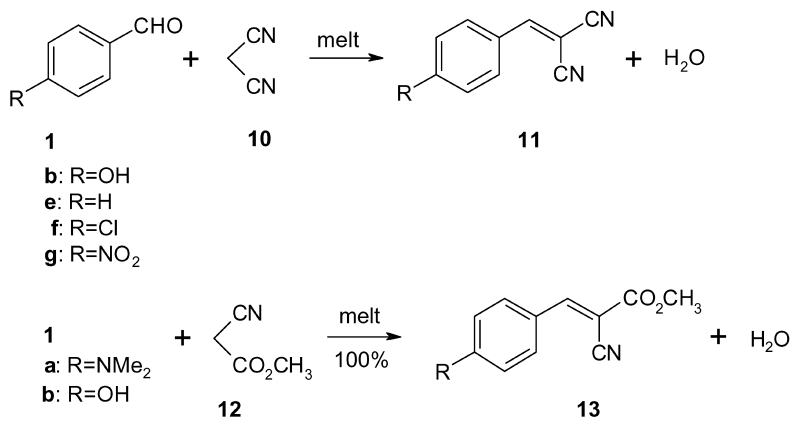
The electron-poor alkenes **3**, **5**, **9**, **11**, and **13** are useful intermediates for Michael additions. These are frequently performed in solution under base catalysis,[33] but even solvent-free versions at base,[34] acid[35] or Lewis acid[36] catalysis were never quantitative and required chromatographic purification techniques. This poor situation did not change when dry solid supports and microwave heating were applied.[37] However, stoichiometric solid mixtures or melts were not tried in the absence of both catalysts and microwave irradiation. We reacted **11b**,**e**,**f**,**g** with dimedone (**6**) in stoichiometric melts without any catalyst and obtained quantitative yields of **14b**,**e**,**f**,**g** in a waste-free manner. These compounds were previously obtained under catalysis with acids or bases though with lower yields[38–43] (Table 3). The NMR-data of **14** are typical for this type of

Table 2. Reactions of **1** with **8**, **10** and **12**; reaction conditions, yields, and melting points of the products **9**, **11** and **13**

Product	Reaction condition	Yield (%)	Mp (°C)	Ref. mp (°C)	Ref. reaction condition	Yield (%)
9a	Solid-state, NMe_3, rt, 1 d	100	197	198–199[19]	Et_2NH, ethanol, heating, 1h[19]	83–85[19]
	Melt, 160°C, 1 h	100				
9b	Solid-state, NMe_3, rt, 1d	100	245	245–246[20]	Piperidine, ethanol, heating, 24 h[21]	66[21]
	Melt, 170°C, 1 h	100				
9f	Solid-state, NMe_3, 1 d, rt	100	209	210[22]	$ZnCl_2$, 10 min, 100°C[22]	97[22]
	Melt, 150°C, 1 h	100				
11b	Melt, 150°C, 1 h	100	186–188	183[1a]	Piperidine, ethanol, heating[18]	87[23]
11e	Solid–liquid, 1 h, rt	100	82–84	83–84[24]	Piperidine, ethanol, 10 min, heating[20]	95[25]
	Melt, 150°C, 1 h	100				
11f	Melt, 150°C, 1 h	100	161–162	162[26]	K_3PO_4, ethanol, 0.5 h, 20°C[22]	91[27]
11g	Melt, 150°C, 1 h	100	158–159	158–159[28]	K_3PO_4, ethanol, 0.5 h, 20°C[27]	96[27]
13a	Melt, 170°C, 1 h	100	141–143	140–141[29]	Xonotlite/potassium -*t*-butoxide, 1 h[30]	73[30]
13b	Melt, 170°C, 1 h	100	208–210	211[31]	Piperidine, ethanol, heating[32]	Not reported



Scheme 4. Quantitative synthesis of **9**.



Scheme 5. Quantitative stoichiometric melt reactions to give **11** and **13**.

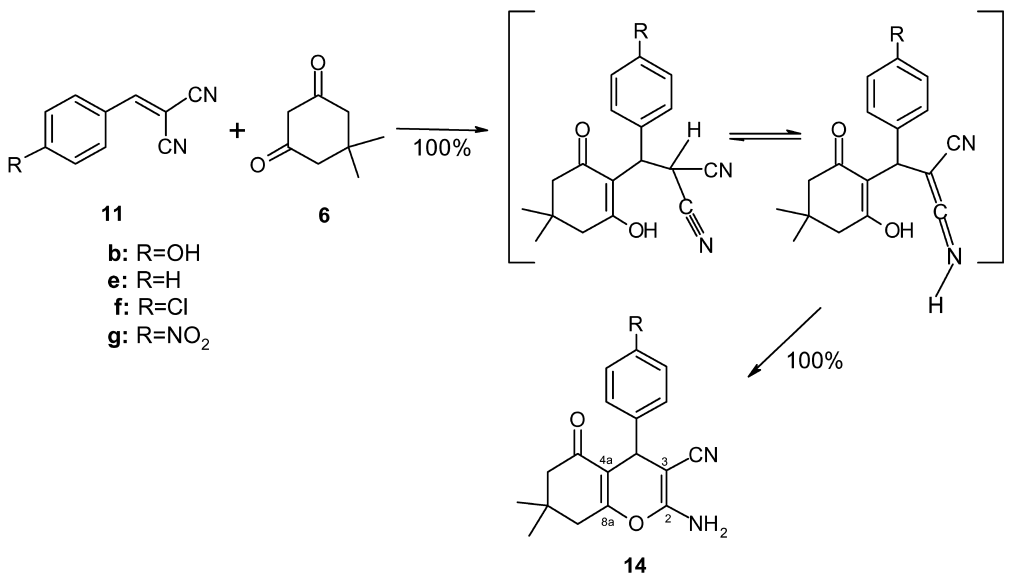
Table 3. Yields and melting points of the products **14b**,**e**,**f**,**g** from **11b**,**e**,**f**,**g** and **6** and reference data

14	Reaction conditions	Yield (%)	Mp (°C)	Ref. mp (°C)	Ref. reaction condition	Ref. yield (%)
b	Melt–solid, 1 h, 97°C	100	222–225	Not reported	Not reported[33,40]	Not reported[33,40]
e	Melt, 1 h, 100°C	100	233–235	233–234[41]	CH_3CN/AcOH (10:1), 2 h, reflux[35]	81[42]; 77[38]
f	Melt, 1 h, 130°C	100	214–216	218[43]	$N(Et)_3$ and EtOH[43]	70[43]; 63[38]
g	Melt, 1 h, 130°C	100	183–185	174–176[38]	Piperidine, microwave, 6 min[38]	85[38]

polar structure. The signals of **14e** for C-2 (δ=157.7) and C-8a (δ=161.3) appear at very high and the signals for C-3 (δ=60.0) and C-4a (δ=113.0) at rather low δ values. Thus, there can be no doubt on the structure of **14** and indeed DFT (B3LYP/6-31G*) calculations predict it more stable than the other thinkable tautomers or the open chain dicyano intermediate (worse by 16.2 kcal mol^{-1}). The electrostatic charges for C-2, C-3, C-4a, C-8a of **14e** were calculated to be 0.594, −0.547, −0.535, and 0.394, respectively, and that explains the strong high-field shift of the ^{13}C NMR signals of C-2 and C-8a as well as the low-field shift of C-3 and C-4a[40] when compared to 'normal' olefinic carbons (Scheme 6).

3. Conclusions

A major improvement is achieved if Knoevenagel condensations are performed in the solid state or solvent-, catalyst-, and support-free in the stoichiometric melt. The reported reactions proceed quantitatively and waste-free. Furthermore, no microwave irradiation is required. Also Michael additions of the now easily prepared electron-poor alkenes (to give for example **7** and **14**) profit from the stoichiometric melt technique without any auxiliary. The gaseous catalyst NMe_3 in the room temperature solid-state syntheses of **9a**,**b**,**f** (that can be avoided at 150–170°C in the melt) is a comparably minor complication that may be tolerated, as it



Scheme 6. Quantitative Michael addition reactions of **11** with **6** followed by rearrangement and cyclization to give **14** in three-cascades.

is easily removed from the product by evaporation. The recovery of NMe_3 from the water of reaction is feasible for larger runs. The most important advance is the non-requirement of purifying workup if pure starting materials are used, as usual. All of the 23 useful electron-poor olefins and their Michael adducts are now more easily available and even large scale waste-free syntheses have been demonstrated (**3b**,**c**). Thus, the synthetic value of the building blocks **3**, **5**, **9**, **11**, and **13** has much increased by the sustainable syntheses techniques without microwave and solid support or solvents and catalysts.

4. Experimental

4.1. General methods

Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Perkin–Elmer 1720-X FT-IR spectrometer using potassium bromide pellets. 300 MHz ^{1}H NMR and 75.5 MHz ^{13}C NMR spectra were recorded on a Bruker WP 300 spectrometer. The chemical shifts are reported in ppm (δ-scale) relative to internal TMS and coupling constants are reported in Hertz (Hz). $CDCl_3$/[D_6]-DMSO mixtures contained up to 20% [D_6]DMSO. Mass spectra were obtained at a Finnigan MAT 212 System. Uniform heating of the stoichiometric melts without partial distillation or sublimation was obtained in closed flasks in a preheated oven. The ball-mill for 2 mmol runs was a Retsch MM 2000 swing mill with a 10 mL stainless steel double-walled beaker with fittings for circulating coolants. Two stainless steel balls with 12 mm diameter were used. Ball-milling was performed at 20–25 Hz frequency usually at room temperature (without circulating liquid the temperature did not rise above 30°C). Water of the appropriate temperature was circulated for heating or cooling. The 200 g batches were milled in a water-cooled 2 L Simoloyer® CM01-2RM-S1 horizontal high-grade steel ball-mill with stellite rotor and 2 kg CR6 balls with 5 mm diameter. Completeness of the solid-state reactions was checked by IR spectroscopy in KBr, product purity by melting point and ^{1}H NMR spectroscopy. B3LYP (basis set 6-31G*) calculations with full geometry optimisation were performed with the program TITAN, version 1.01, of Wavefunction, Inc., Irvine, USA.

4.2. General procedure for the preparation of 3

Small scale. The barbituric acid **2** (2.00 mmol) and the solid aldehyde **1** (2.00 mmol) were ball-milled for the time given in Table 1 at the indicated temperature. The solid powders were dried at 80°C in a vacuum to give pure **3** with 100% yield and did not require purifying workup.

Large scale. 200 g quantities of stoichiometric 1:1-mixtures of the loosely premixed crystalline reaction partners were fed to the Simoloyer® ball-mill. The rotor was run at 1200 min^{-1} for 1 h and the products were milled out for 10 min at frequently changing rotor frequencies of 900 and 1200 min^{-1}. The temperature was 18°C at the walls with a maximum of 20°C for **3b** (with water cooling) and 50°C for **3c** (without cooling) in the center of the Simoloyer®. The solid powders were dried at 80°C in a vacuum to give pure product with 100% yield from the second run and did not require purifying workup. The last run left some hold-back that should be quantitatively expelled to a cyclone with an internal gas cycle.[44]

4.2.1. 1,3-Diethyl-5-[4-(dimethylamino)benzylidene]-2-thiobarbituric acid (3a). Mp 207–209°C, lit.[13] 204–208°C; IR (KBr): ν=2976, 1684, 1651, 1611, 1504, 1369 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ=8.41 (s and ψd, 3H), 6.70 (ψd, 2H), 4.60 (q, 2H, J=7 Hz), 4.58 (q, 2H, J=7 Hz), 3.20 (s, 6H), 1.33 (t, 3H, J=7 Hz), 1.31 (t, 3H, J=7 Hz), ^{13}C NMR ($CDCl_3$), δ=178.9, 162.2, 159.8, 159.4, 154.7, 139.9 (2C), 121.7, 111.2 (2C), 110.4, 43.9, 43.4, 40.1 (2C), 12.5, 12.4.

4.2.2. 1,3-Dimethyl-5-(4-hydroxybenzylidene)-barbituric acid (3b). Mp 297°C, lit.[14] 297–298°C; IR (KBr): ν=3201, 1667, 1641, 1609, 1531, 1510, 1420, 1387 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=10.5 (broad signal, 1 OH), 8.35 (s, 1H), 8.28 (ψd, 2H), 6.89 (ψd, 2H), 3.30 (s, 6H); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=163.2, 162.5, 160.6, 160.6, 157.0, 150.8, 138.1 (2C), 123.6, 115.3 (2C), 28.3, 27.7.

4.2.3. 5-(4-Hydroxy-benzylidene)-pyrimidine-2,4,6-trione (3c). Mp 299–301°C, lit.[15] >300°C; IR (KBr): ν=3196, 1716, 1697, 1665, 1610, 1531, 1508, 1444, 1407, 1280, 1178 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=11.20 (broad signal, NH), 11.08 (broad signal, NH), 10.55 (broad signal, OH), 8.33 (ψd, 2H), 8.30 (s, 1H), 6.88 (ψd, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=163.0, 162.1, 161.0, 155.5, 149.0, 137.2 (2C), 122.6, 114.3 (2C), 112.2.

4.2.4. 5-(4-Hydroxy-3-methoxybenzylidene)-barbituric acid (3d). Mp 313°C, lit.[17] 287–289°C; IR (KBr): ν=3278, 3065, 1747, 1699, 1662, 1575, 1538, 1504, 1434, 1402 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=11.12 (broad signal, NH), 10.0 (broad signal, NH), 8.55 (s, 1H), 8.31 (s, 1H), 7.78 (ψd, 1H), 6.93 (ψd, 1H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=162.8, 160.9, 155.4, 151.8, 148.7, 145.5, 131.5, 122.9, 116.3, 113.8, 111.9, 54.1.

4.3. General procedure for the preparation of 5

Meldrum's acid (**4**) (2.00 mmol) and the solid aldehyde **1** (2.00 mmol) were ball-milled at 50°C for 1 h. The solid powders were dried at 80°C in a vacuum to give pure **5** with 100% yield.

4.3.1. 5-(4-Dimethylaminobenzylidene)-1,1-dimethyl-4,6-dioxo-1,3-dioxane (5a). Mp 162°C, lit.[18] 162–164; IR (KBr): ν=1700, 1613, 1542, 1506, 1372, 1290, 1162 cm^{-1}; ^{1}H NMR($CDCI_3$/DMSO-d_6), δ=8.31 (s, 1H), 8.22 (ψd, 2H), 6.71 (ψd, 2H), 3.11 (s, 6H), 1.72 (s, 6H); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=165.2, 161.4, 158.0, 154.5, 138.9 (2C), 120.2, 111.3 (2C), 105.1, 103.4, 40.0 (2C), 27.3 (2C).

4.3.2. 5-(4-Hydroxybenzylidene)-1,1-dimethyl-4,6-dioxo-1,3-dioxane (5b). Mp 193°C, lit.[18] 192–194°C; IR (KBr): ν=3273, 1748, 1697, 1586, 1574, 1450, 1394, 1278 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=10.62 (broad signal, 1NH), 8.26 (s, 1H), 8.12 (ψd, 2H), 6.90 (ψd, 2H), 1.76 (s,

6H); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=162.7, 162.2, 158.9, 156.2, 136.6 (2C), 121.8, 114.6 (2C), 108.0, 102.2, 25.8 (2C).

4.4. General procedure for the preparation of 7

Dimedone (**6**) (4.00 mmol) and the solid aldehyde **1** (2.00 mmol) were ball-milled at 50°C (**1e** at 100°C) for 1 h. The solid powders were dried at 80°C in a vacuum to give a quantitative yield of pure **7**. If the ratio of **1** and **6** was chosen to be 1:1 only the products **7** and unused aldehyde **1** (but not the intermediate Knoevenagel product) could be obtained and analysed by NMR spectroscopy under these reaction conditions.

4.4.1. 2,2′-(4-Hydroxyphenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one) (7b). Mp 189°C, lit.[18] 190–192°C; IR (KBr): ν=3423, 2963, 1596, 1514, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ=11.82 (broad signal, 2 OH), 6.89 (ψd, 2H), 6.65 (ψd, 2H), 5.43 (s, 1H), 2.40 (m, 8H), 1.20 (s, 6H), 1.09 (s, 6H); ^{13}C NMR ($CDCl_3$), δ=190.6 (2C), 189.5 (2C), 153.8, 129.6, 127.9 (2C), 115.8 (2C), 115.2 (2C), 47.0 (2C), 46.4 (2C), 32.0, 31.4 (2C), 29.5 (2C), 27.4 (2C).

4.4.2. 2,2′-Phenylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one) (7e). Mp 190–191°C, lit.[18] 188–190°C; ^{1}H NMR ($CDCl_3$), δ=11.80 (broad signal, OH), 7.20 (m, 2H), 7.12 (ψd, 1H), 7.05 (ψd, 2H), 5.48 (s, 1H), 2.35 (m, 8H), 1.16 (s, 6H), 1.08 (s, 6H); ^{13}C NMR ($CDCl_3$), δ=190.4 (2C), 189.4 (2C), 138.1, 128.2 (2C), 126.8 (2C), 125.8, 115.6 (2C), 47.1 (2C), 46.5 (2C), 32.7, 31.4 (2C), 29.6 (2C), 27.4 (2C).

4.4.3. 2,2′-(4-Chlorophenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one) (7f). Mp 139°C, lit.[18] 140–142°C; IR (KBr): ν=2957, 1593, 1491, 1375, 1305, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ=11.81 (broad signal, 2 OH), 7.20 (ψd, 2H), 7.01 (ψd, 2H), 5.48 (s, 1H), 2.39 (m, 8H), 1.18 (s, 6H), 1.08 (s, 6H); ^{13}C NMR ($CDCl_3$), δ=190.6 (2C), 189.4 (2C), 136.7, 131.6, 128.3 (2C), 128.2 (2C), 115.3 (2C), 47.0 (2C), 46.4 (2C), 32.4, 31.4 (2C), 29.5 (2C), 27.4 (2C).

4.4.4. 2,2′-(4-Nitrophenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one) (7g). Mp 189°C, lit.[18] 188–190°C; IR (KBr): ν=2959, 1593, 1513, 1376, 1345 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ=11.74 (broad signal, 2 OH), 8.11 (ψd, 2H), 7.21 (ψd, 2H), 5.50 (s, 1H), 2.40 (m, 8H), 1.19 (s, 6H), 1.11 (s, 6H); ^{13}C NMR ($CDCl_3$), δ=190.8 (2C), 189.5 (2C), 146.5, 146.1, 127.6 (2C), 123.5 (2C), 114.9 (2C), 47.0 (2C), 46.4 (2C), 33.3, 31.5 (2C), 29.5 (2C), 27.4 (2C).

4.5. General procedure for the preparation of 9

Solid-state reaction. Cyanoacetamide (**8**) (2.00 mmol) and the solid aldehyde **1** (2.00 mmol) were ball-milled for 10 min. The powder was treated with trimethylamine (1 bar) in a 250 mL flask for 24 h. The catalyst and the water of the reaction were removed at 100°C in a vacuum to give a quantitative yield of pure **9** without requiring purifying workup.

Melt reaction. Stoichiometric mixtures of **1a**,**b**,**f** (2.00 mmol) with **8** (2.00 mmol) were melted under vacuum in a 50 mL flask at the temperatures reported in Table 2 for the times given. **9a**,**b**,**f** were quantitatively obtained after drying as above.

4.5.1. 4-Dimethylaminobenzylidene cyanoacetamide (9a). Mp 197°C, lit.[19] 198–99°C; IR (KBr): ν=3406, 3154, 2200, 1680, 1610, 1562, 1523 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=8.02 (s, 1H), 7.89 (ψd, 2H), 7.0 (broad signal, 2 NH), 6.71 (ψd, 2H), 3.11 (s, 6H); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=163.0, 152.0, 150.8, 132.1 (2C), 118.2, 117.5, 110.4 (2C), 95.0, 38.8 (2C).

4.5.2. 4-Hydroxybenzylidene cyanoacetamide (9b). Mp 245°C, lit.[20] 245–46°C; IR (KBr): ν=3452, 3365, 3190, 2215, 1706, 1679, 1575 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=8.08 (s, 1H), 7.82 (ψd, 2H), 7.20 (broad signal, 1 OH), 6.89 (ψd, 2H), 5.98 (broad signal, 2 NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=162.2, 161.2, 150.6, 131.9 (2C), 121.8, 116.5, 115.2 (2C), 98.9.

4.5.3. 4-Chlorbenzyliden cyanoacetamide (9f). Mp 209°C, lit.[22] 210°C; IR (KBr): ν=3455, 3156, 2212, 1703, 1588 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=8.16 (s, 1H), 7.95 (ψd, 2H), 7.72 (s, 2 NH), 7.52 (ψd, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=161.5, 150.8, 138.1, 131.3 (2C), 129.9, 129.0 (2C), 116.2, 104.6.

4.6. General procedure for the preparation of 11

The stoichiometric mixtures of **1b**,**e**,**f**,**g** (2.00 mmol) with **10** (2.00 mmol) were melted under vacuum in a 50 mL flask in a drying oven at the temperatures given in Table 2 for the times given. **11b**,**e**,**f**,**g** were quantitatively obtained, after drying at 100°C in a vacuum and did not require purifying workup. The melting points and spectroscopic data of the products **11** corresponded to the published data (see Table 2).

4.6.1. 4-Hydroxybenzylidene malononitrile (11b). Mp 186–188°C, lit.[1a] 183°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=10,42 (broad signal, 1 OH), 7.85 (ψd, 2H), 7.68 (s, 1H), 6.94 (ψd, 2H), 5.98 (broad signal, 2 NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=163.9, 159.0, 133.4 (2C), 122.4, 116.5 (2C), 114.4, 113.4, 75.8.

4.6.2. Benzylidene malononitrile (11e). Mp 82–84°C, lit.[24] 83–84°C; ^{1}H NMR ($CDCl_3$), δ=7.90 (ψd, 2H), 7.80 (s, 1H), 7.65 (ψd, 1H), 7.55 (m, 2H); ^{13}C NMR ($CDCl_3$), δ=159.9, 134.6, 130.9, 130.7 (2C), 130.1 (2C), 113.7, 112.5, 82.8.

4.6.3. 4-Chlorobenzylidene malononitrile (11f). Mp 161–162°C, lit.[26] 162°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=7.79 (s, 1H), 7.69 (ψd, 2H), 7.33 (ψd, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=158.4, 140.3, 131.4 (2C), 129.4 (2C), 129.0, 113.0, 112.0, 82.4.

4.6.4. 4-Nitrobenzylidene malononitrile (11g). Mp 158–159°C, lit.[28] 158–159°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=8.40 (ψd, 2H), 8.32 (s, 1H), 8.14 (ψd, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ=157.5, 149.1, 135.4, 130.6 (2C), 123.3 (2C), 112.0, 111.0, 85.5.

4.7. General procedure for the preparation of 13

The stoichiometric mixtures of **1a**,**b** (2.00 mmol) with **12** (2.00 mmol) were melted under vacuum in a 50 mL flask in a drying oven at the temperatures reported in Table 2 for the times given. **13a** and **13b** were quantitatively obtained after drying at 80°C in a vacuum and did not require purifying workup. The products **13a**,**b** were identical in all respects with those described in the literature (see Table 2).

4.7.1. 4-Dimethylaminobenzylidene methylcyanoacetate (13a). Mp 141–143°C, lit.[29] 140–141°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=8.10 (s, 1H), 7.94 (ψd, 2H), 6.70 (ψd, 2H), 3.90 (s, 3H), 3.11 (s, 6H); ^{13}C NMR ($CDCl_3$), δ=164.8, 154.7, 153.7, 134.1 (2C), 119.4, 117.5, 111.5 (2C), 93.6, 52.7, 40.0 (2C).

4.7.2. 4-Hydroxybenzylidene methylcyanoacetate (13b). Mp 208–210°C, lit.[31] 211°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=10.18 (br s, OH), 8.17 (s, 1H), 7.93 (ψd, 2H), 6.95 (ψd, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$), δ=163.7, 162.8, 154.9, 133.8 (2C), 122.8, 116.4 (2C), 116.3, 97.0, 52.8.

4.8. General procedure for the preparation of 14

The stoichiometric mixtures of **11b**,**e**,**f**,**g** (2.00 mmol) with dimedone (**6**) (2.00 mmol) were melted (or ball-milled in the case of **11b**) at the temperatures reported in Table 3 for the times given. **14b**,**e**,**f**,**g** was obtained after drying at 80°C in a vacuum with 100% yield and did not require purifying workup.

4.8.1. 2-Amino-3-cyano-7,7-dimethyl-4-(4-hydroxyphenyl)-5-oxo-5,6,7,8-tetra-4*H*-chromene (14b). Mp 222–225°C, lit.[40] not reported; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=8.80 (br s, OH), 7.10 (ψd, 2H), 6.80 (ψd, 2H), 5.86 (br s, 2H, NH_2), 4.31 (s, 1H, H-4), 2.54 (br s, 2H, H-8), 2.30 (H-6a, J_{AB}=16.0 Hz), 2.22 (H-6b, J_{AB}=16.0 Hz, 1.18 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$), δ=195.2 (C=O), 160.8 (C-8a), 157.6, 155.4 (C-2), 134.1, 127.7 (2C), 119.0 (CN), 114.6 (2C), 113.4 (C-4a), 60.5 (C-3), 50.0 (C-6), 39.8 (C-8), 34.1 (C-4), 31.3 (C-7), 28.1, 26.8.

4.8.2. 2-Amino-3-cyano-7,7-dimethyl-4-phenyl-5-oxo-5,6,7,8-tetra-4*H*-chromene (14e). Mp 233–235°C, lit.[41] 233–234°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=7.30–7.10 (m, 5H), 5.85 (broad signal, 2H, NH_2), 4.32 (s, 1H, H-4), 2.48 (br s, 2H, H-8), 2.25 (H-6a, J_{AB}=16.0 Hz), 2.15 (H-6b, J_{AB}=16.0 Hz), 1.10 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$), δ=195.1 (C=O), 161.3 (C-8a), 157.7 (C-2), 143.3, 127.6 (2C), 126.7 (2C), 126.0, 118.8 (CN), 113.0 (C-4a), 60.0 (C-3), 49.9 (C-6), 39.9 (C-8), 35.0 (C-4), 31.3 (C-7), 28.1, 26.8.

4.8.3. 2-Amino-3-cyano-7,7-dimethyl-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetra-4*H*-chromene (14f). Mp 214–216°C, lit.:[42] 218°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=7.30–7.10 (m, 4H), 6.30 (br s, 2H, NH_2), 4.28 (s, 1H, H-4), 2.46 (br s, 2H, H-8), 2.24 (H-6a, J_{AB}=16.0 Hz), 2.14 (H-6b, J_{AB}=16.0 Hz), 1.12 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$), δ=194.6 (C=O), 161.1 (C-8a), 157.5 (C-2), 141.9, 130.9, 127.9 (2C), 127.2 (2C), 118.4 (CN), 112.1 (C-4a), 58.1 (C-3), 49.4 (C-6), 38.9 (C-8), 34.2 (C-4), 30.9 (C-7), 27.6, 26.3.

4.8.4. 2-Amino-3-cyano-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetra-4*H*-chromene (14g). Mp 183–185°C, lit.[38] 174–176°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6), δ=8.14 (ψd, 2H), 7.42 (ψd, 2H), 6.50 (br s, 2H, NH_2), 4.48 (s, 1H, H-4), 2.52 (br s, 2H, H-8), 2.26 (H-6a, J_{AB}=16.0 Hz), 2.16 (H-6b, J_{AB}=16.0 Hz), 1.14 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$), δ=195.2 (C=O), 162.1 (C-8a), 158.1 (C-2), 150.9, 146.2, 128.1 (2C), 123.1 (2C), 118.1 (CN), 112.2 (C-4a), 58.5 (C-3), 49.9 (C-6), 40.1 (C-8), 35.4 (C-4), 31.6 (C-7), 28.2, 27.0.

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