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COMMUNICATION

CO_2 Assisted Synthesis of Non-symmetric α-Diketones Directly from Aldehydes via C-C Bond Formation

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Pradipbhai Hirapara, Daniel Riemer, Nabanita Hazra, Jignesh Gajera, Markus Finger, and Shoubhik Das*

CO_2 assisted various symmetric and non-symmetric α-diketones have been synthesized directly from the corresponding aldehydes using transition metal-free catalysts. This method even can be applied to synthesize pharmaceuticals directly from aldehydes. The crucial role of CO_2 has been investigated in detail and mechanism is proposed on the basis of experiments and DFT calculations.

α-Diketones are highly important structural moieties and have been widely used as building blocks for synthesis of fine chemicals and pharmaceuticals.[1] Traditional synthesis of these α-diketones relies on oxidation of alkenes, alkynes, acyloins and 1,2-hydroxy compounds.[2-5] Additionally, oxidative cleavage of 1,3-diketones, α,β-epoxy ketones and α,β-unsaturated ketones are also known for the synthesis of α-diketones.[6] Unfortunately, these methodologies have major drawbacks such as harsh reaction conditions, low product yields and narrow substrates scope. Moreover, synthesis of non-symmetric α-diketones *via* above-mentioned methods requires the corresponding non-symmetric starting materials and therefore further steps and tedious purifications. In contrast, direct synthesis of non-symmetric α-diketones from aldehydes via C-C bond formation will be an attractive alternative.[7] It reduces formation of possible toxic by-products and provides access to numerous α-diketones starting from commercially available aldehydes.

Inspired by this idea, we investigated the use of substituted N-heterocyclic carbenes (NHC) that are known to form C-C bonds.[8] In this respect, we were especially interested to apply CO_2 as a soft promoter. In the last two decades, a number of transition metal-based catalysts and transition metal-free homogeneous reactions have been discovered that apply CO_2 either as building block or promoter in sustainable syntheses of pharmaceutical products and fine chemicals.[9] It should be noted that activation of CO_2 is highly challenging due to its strong thermodynamic and kinetic stability.[10-11] On the other hand, utilizing CO_2 as a soft promoter only has been achieved by heterogeneous catalysts for oxidative dehydrogenation, oxidative coupling and oxidation of alkanes.[12] To the best of our knowledge, homogeneous catalysts have been explored rarely to use CO_2 as a soft promoter in organic reactions.[13] Based on all these information, herein we report CO_2 promoted synthesis of symmetric and non-symmetric α-diketones directly from the corresponding aldehydes using NHC based catalysts.[14]

At the outset of our reactions, a variety of NHC catalysts (10 mol%) along with different bases have been applied to optimize the reaction conditions for the synthesis of furil directly from furfural under CO_2 atmosphere (**Table 1**, supporting information). Indeed, in presence of 1.5 eq. of K_2CO_3, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride as catalyst (10 mol%) showed 49% of product formation in DMSO at 55 °C after 16 h. To our delight, changing catalyst to cheaper 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide increased formation of furil to 86% within 16 h. In fact, even on a 5 *g*-scale 80% furil was isolated without any further precautions. Other bases such as Cs_2CO_3, KOH, KO^{t}Bu, DMAP showed less activity at the same reaction conditions. Also, a decrease of base loading from 1.5 to 0.5 eq. gave significantly lower yield of the product. No formation of product was observed in absence of base and/or catalyst. The essential role of CO_2 in this reaction has been proven under N_2 and O_2 atmosphere (without the presence of CO_2) when the formation of product was negligible (**Table 1**, supporting information).

With these optimized conditions in hand, the scope of this reaction protocol was explored (**Scheme 1**). A number of aromatic and hetero-aromatic aldehydes were converted to the corresponding α-diketones. Electron-donating as well as electron-withdrawing groups on the rings were well tolerated and leaded to good yields up to 83% (**Scheme 1**, **4–6**). Also, hetero-aromatics (**Scheme 1**, **7–10**) and condensed aromatic rings (**Scheme 1**, **12**) gave excellent yields up to 82%. It was also noteworthy that the reaction proceeded smoothly for both substitution types on the furan and thiophene ring (**Scheme 1**, **1**, **3**, and **7–8**).

Further application of symmetric α-diketones was also explored, particularly from 4,4'-dichlorobenzil (**Scheme 1**, **5**). It should be noted that commercially available 4,4'-dichlorobenzil is highly expensive such as from Sigma Aldrich (119 €/10 mg), AK Scientific (717 €/5 g), Fluorochem (430 €/5 g) or TCI (319 €/5 g). To our delight, the synthesis of 4,4'-dichlorobenzil can be achieved using a cheap catalyst and reagents in 5 *g*-scale with 80% yield. Based on this reagent, a number of commercially interesting compounds were successfully synthesized, i.e. pharmaceutically active molecules **14** (a neuroprotective agent) and **15** (an antimalarial agent)[15] or **16** which is an important precursor for graphene nanoribbons that helps to improve the properties of organic electronic materials in polymer blends (**Scheme 2**).[16]

Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstr. 2, Göttingen, Germany
E-mail: shoubhik.das@chemie.uni-goettingen.de
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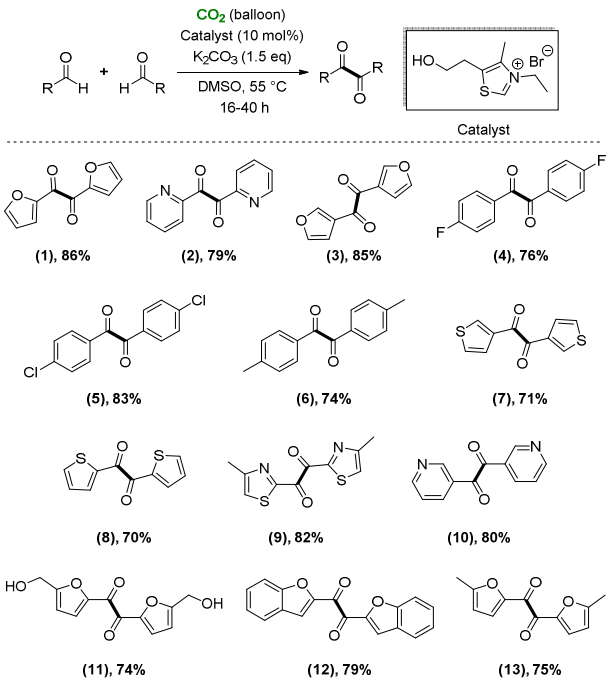
Scheme 1: Synthesis of α-diketones directly from aldehydes.

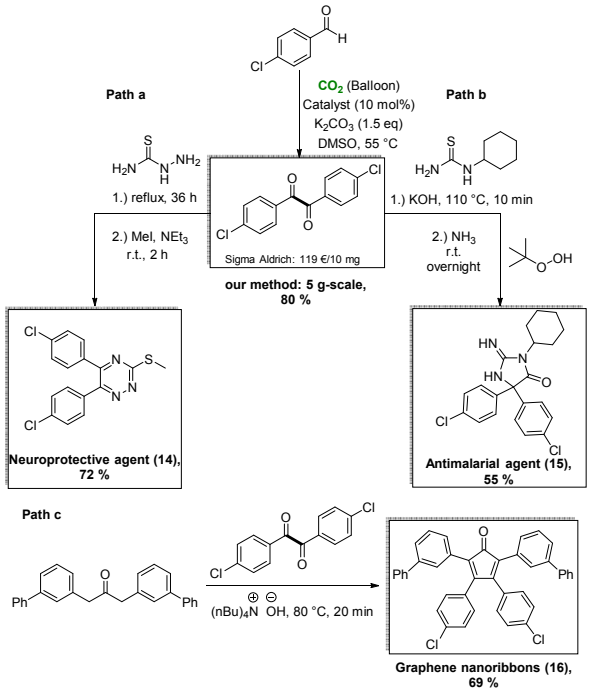


Reaction conditions: Substrates (0.5 mmol), K_2CO_3 (1.5 eq), catalyst (10 mol%), DMSO (2.5 mL), CO_2 (balloon), 55 °C, 16–40 h. All are isolated yields.

As another promising aspect, a number of aldehydes such as furfural, hydroxymethylfurfural (HMF) or 5-methyl furfural are available from carbohydrates in large scale by many well-known methods. Carbohydrates are the major component of biomass, one of the most abundant renewable resources, which has got significant priority for the production of fuels and fine chemicals.[17] Using our reaction methodology, these aldehydes can be converted to the corresponding α-diketones (**Scheme 1**; **1**, **11** and **13**). E.g. furil (**1**) can be synthesized directly from furfural without any purification issue. Later it can be transformed into 2,3-di(furan-2-yl)quinoxaline (**17**), which was found to slow down the corrosion rate of mild steel in H_2SO_4 (**Scheme 3**).[18a] A pyrazine derivative (**18**), prevalent in flavors, numerous biologically active substances and agrochemicals, could be generated from furil as well.[18b] Through CuI catalyst and air-promoted oxidative cyclization it was also possible to synthesize an oxazole derivative (**19**), an important scaffold for pharmaceuticals and functional materials.[18c] We successfully converted furil to an antitumor active compound (**20**) that was found to have the highest activity against a panel of cancel cell lines.[18d] Moreover, imidazole (**21**) can also be synthesized from furil, benzaldehyde and ammonium acetate.[18e] Imidazoles in general are important building blocks for the synthesis of antitumor, antibiotic, antifungal, anti-inflammatory and anti-allergic drug molecules. To the best of our knowledge, there was no such report for the direct conversion of biomass-derived furfural into wide utilizable chemicals and pharmaceuticals.

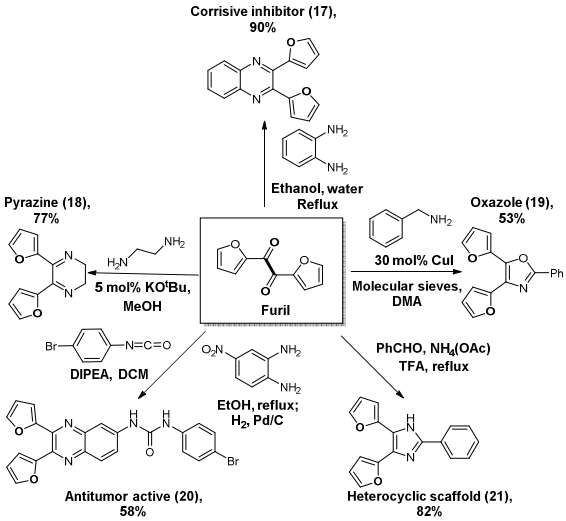
We also investigated the applicability of the new protocol for the synthesis of non-symmetric α-diketones. For this purpose, we started with a 1:1 ratio of the two different aldehydes but obtained mixtures of products with poor product selectivity. However, changing of the aldehydes ratio to 1:1.5 increased the selectivity in all cases (**Scheme 4**).[19,20] It must be noted that formation of the homo α-diketones as by-products could not be suppressed completely. To our delight, α-diketones having different hetero-aromatics (**Scheme 4**, 22–23, 30–32), α-diketones having electron-withdrawing/electron-donating groups (**Scheme 4**, 26), and α-diketones having aromatic/hetero-aromatic (**Scheme 4**, 24–25 and 27) can be obtained in an excellent yield. Notably, none of these non-symmetric α-diketones are commercially available and traditional synthesis relies on two to three steps syntheses. Finally, non-symmetric α-diketones were also obtained directly from biomass-derived aldehydes in an excellent yield (**Scheme 4**, 28–29 and 33).

Scheme 2: Synthesis of drug molecules and precursors for graphene nanoribbons from 4,4′-dichlorobenzil.



Reaction conditions: 1. Path a: 1.) 4,4′-dichlorobenzil (0.5 mmol), thiosemicarbazide (1.0 mmol), EtOH, reflux, 40 h; 2.) MeI (1.2 eq), NEt_3 (7.2 eq), MeOH, r.t. 2 h; path b: 1.) cyclohexylthiourea (0.58 mmol), 4,4′-dichlorobenzil (0.52 mmol), KOH (0.8 mmol), water/DMSO, 110°C, 10 min; 2.) NH_3, *t*Bu hydroperoxide, water/MeOH, r.t. overnight. Path c: Substrate (0.22 mmol), $(nBu)_4NOH$ (0.22 mmol), ^{t}BuOH, 80°C, 20 min; All are isolated yield.

Scheme 3: Conversion of biomass-derived furil to utilizable chemicals.



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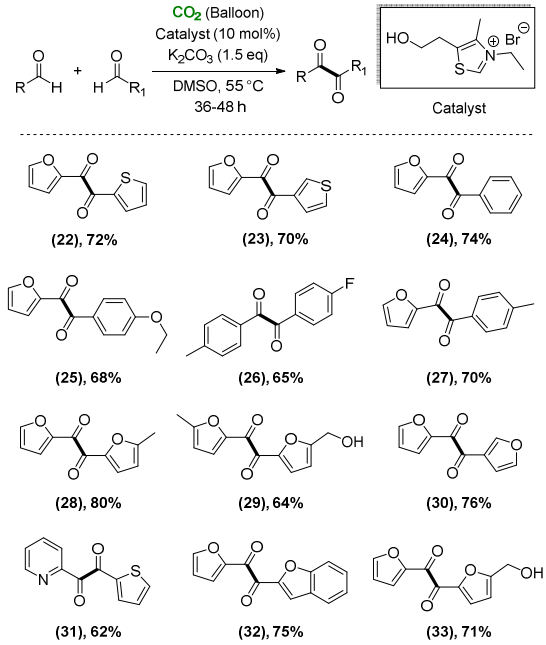
Scheme 4: Synthesis of non-symmetric α-diketones directly from two different aldehydes.

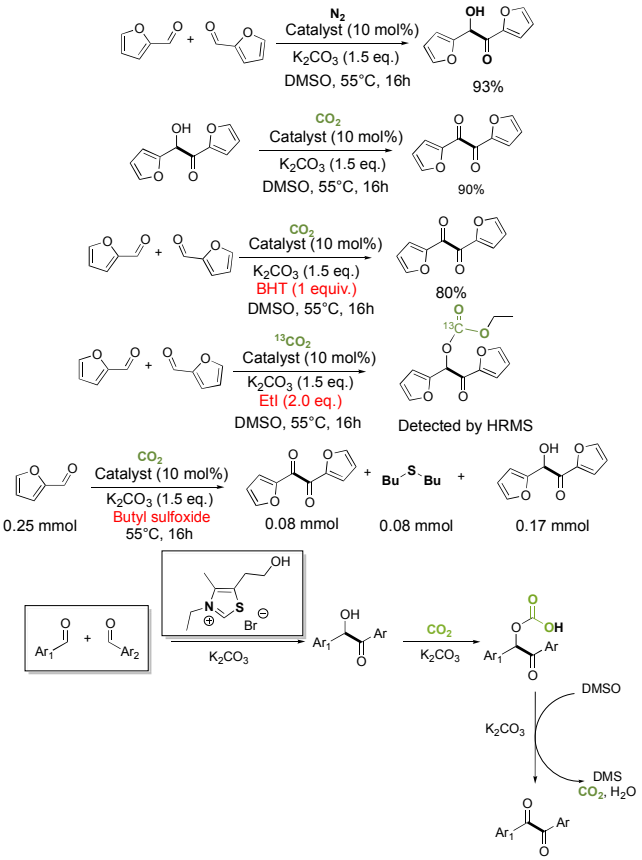


Reaction conditions: Substrates (0.25 mmol and 0.375 mmol, respectively), K_2CO_3 (1.5 eq), catalyst (10 mol%), DMSO (2.5 mL), CO_2 (balloon), 55 °C, 36–48 h. All are isolated yields.

Considering the broad scope of this new approach, we investigated its mechanism. Initial role of the base here (K_2CO_3) is to generate of the free carbene *in situ* that acts as the actual catalyst in the benzoin condensation. Indeed, following the conversion of furfural with progress of time under the optimized reaction conditions showed that furfural was converted to furoin by the catalyst within the first hour while later furoin was slowly oxidized under CO_2 atmosphere to the desired furil (**Figure 1**, supporting information). Under N_2-atmosphere exclusively furoin was formed which was completely converted to furil under CO_2 atmosphere in a separate step (**Scheme 5**). To address the nature of the oxidant further, *in situ* gas GC and NMR measurements were utilized to determine reduced products from CO_2 such as CO, HCOOH or $HCOO^-$. However, only CO_2 as single peak was found in *in situ* gas GC measurement. Additionally, the missing peak of O_2 in these experiments excluded presence of exogeneous O_2 as possible oxidant. Apparently, DMSO acts as oxidizer but the corresponding reduced product dimethyl sulfide could not be quantified due to its low boiling point (31°C).[21] For this purpose, butyl sulfoxide was used. With this replacement, the final reduced product, dibutyl sulfide (boiling point: 189°C) was quantified and found to have equal ratio with the product furil (**Scheme 5**).

Finally, in presence of dibutylhydroxytoluene (BHT, radical scavenger), neither the reaction was slowed down nor stopped and in fact 80% product was isolated, ruling out a radical pathway. If CO_2 is not the oxidant, the question as to its actual role remains open. It is well known from literature that CO_2 can bind to the hydroxy group of the furoin to form the corresponding O-carboxylated intermediate.[22] Direct recognition of this O-carboxylated intermediate was not successful. However, in presence of $^{13}CO_2$ and ethyl iodide the corresponding ethyl carbonate product was detected by HRMS (**Scheme 5**). To sum up, the reaction proceeds in two independent steps, first carbene catalyzed benzoin condensation reaction between two aldehydes followed by a considerable slower but selective, CO_2-promoted oxidation of the benzoin product by DMSO.

Scheme 5: Experimental evidence for the crucial role of CO_2 in the oxidation step.



The role of CO_2 in the oxidation step was further investigated by means of DFT calculations (**Scheme 6**) including alternative pathways (see supporting information). The most realistic scenario is that by formation of an intermediate carboxylate, the hydroxyl group is transformed to a good leaving group prone to nucleophilic attack by DMSO.[20] Formation of the ester is energetically uphill and explains why it could not be detected experimentally. The following rate determining step can either proceed stepwise (S_N1) or in a concerted fashion (S_N2). Considering that both the energy of the intermediate charge separated ion pair (S_N1) or the (gas phase) free energy of the transition state (S_N2) are methodically overestimated, it is safe to assume that the calculated value of 29.4 kcal/mol provides an upper limit that however agrees well with the experimental time frame (16 h). Once the intermediate sulfonium has formed, deprotonation and fast proton transfer under formation of the dimethyl sulfide lead to the diketone. Interestingly, if DMSO is used as an oxidation agent it needs to be activated by a strong electrophile such as oxalyl chloride (Swern), dicyclohexylcarbodiimide (Pfitzner- Moffatt) or others.[21] In contrast, CO_2 is a very mild and sustainable reagent that activates the alcohol.

Scheme 6: Calculated pathway of the CO_2-promoted oxidation step (B3LYP/def2-TZVPP, COSMO(DMSO) corrected single point energies).

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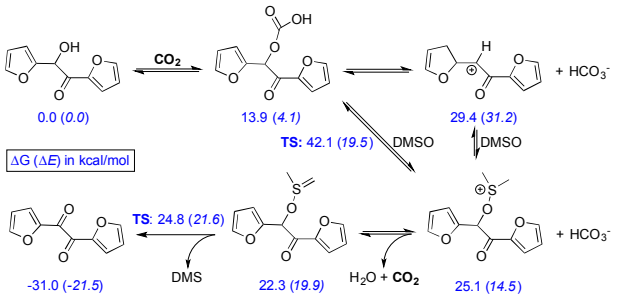

Conclusions

In conclusion, we have demonstrated an efficient and sustainable synthesis of symmetric and non-symmetric α-diketones directly from aldehydes using CO_2 as a promoter. This methodology has shown broad substrates scope along with wide applications towards the synthesis of pharmaceuticals and fine chemicals. Many of these α-diketones are currently expensive or commercially not available but can easily be accessed using our cheap and commercially available catalysts and reagents. We believe this methodology could find interest in the synthesis of highly functionalized molecules, in the synthesis of natural products and pharmaceuticals.

Conflicts of interest

There are no conflicts to declare.

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[20] Under nitrogen atmosphere we observed 1:1 ratio of mix cross benzoin products together with homo products and then when we released CO_2 atmosphere generated our desired product. We have observed the reactivity of our catalyst in this following order: furfural>5-methyl furfural>HMF>Benzofuran aldehyde. For the cross products formation, we took lowest reactive partner in higher ratio than the highest reactive partner and that gave us the best yield after examining all other possibilities. This ratio is highly important for the selective formation of cross-products.

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