

Asymmetric ketones intermediates by cross-ketonization

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Significance and Relevance

This work demonstrates that the selective cross-ketonization of acid/esters can be exploited as a general synthetic approach to obtain valuable asymmetric ketonic intermediates with a continuous catalytic gas-phase process, thus avoiding the drawbacks of conventional homogeneously catalyzed, batchwise synthetic methods in the liquid-phase. This method achieved conversions of the limiting reactants between 75-85 %, selectivities in respect to the limiting reactants between 84-95 %, and space-time yields between 0.131-0.159 h⁻¹.

Preferred and 2nd choice for the topic: Green chemistry and biomass transformation, renewable resources conversion

Preferred presentation: Oral preferred or Short Oral

Introduction and Motivations

The usefulness of ketonization for the valorization of biomass-derived carboxylic acids (CA) is widely recognized. For instance, it has been recently proposed as a viable way to transform the volatile fatty acids (VFAs, C₄-C₈) obtained via fermentation of wet-waste (e.g., food waste, sewer sludge, animal manure) into sustainable aviation fuel (SAF) precursors¹. Ketonization is also a promising way to produce valuable bio-based wax precursors by coupling the fatty acids (FAs) found in waste animal fat or vegetable oils (C₁₂-C₁₈)². However, despite the recent advance in ketonization-based processes to produce renewable fuels and oleochemicals, the full potential of this reaction has yet to be suitably exploited for the selective synthesis of high added-value chemical intermediates for the pharmaceutical, cosmetic and food industry. As of now, asymmetric ketones containing aromatic moieties are mainly produced by liquid-phase batch processes that co-produce significant amounts of waste (e.g., Friedel-Crafts, Heck, Suzuki, Grignard, Claysen-Schmidt, oxidations with peroxides)³, while the examples of selective cross-ketonization of CAs or esters are relatively scarce⁴. Recently, the synthesis of acetyl furan (AF, a food additive and intermediate in the synthesis of antibiotics) via cross-ketonization between methyl 2-furoate (2-MF) and acetic acid (AA) (both obtainable from renewable resources) was proposed as a more sustainable alternative to conventional synthetic methods⁵.

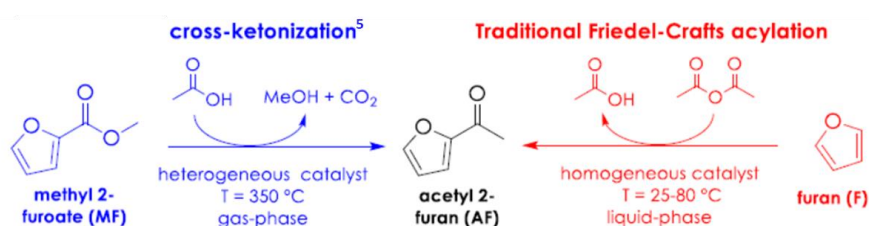


Figure 1 comparison between the gas-phase cross-ketonization pathway towards acetyl furan and the traditional Friedel-Crafts synthesis in the liquid-phase.

Starting from these seminal results, in this work the substrate scope of the gas-phase cross-ketonization approach was further demonstrated by targeting several valuable asymmetric ketones intermediates widely used as chemical intermediates, flavors/fragrances or pharmaceutical precursors (e.g., acetophenone, 4-methyl acetophenone, propiophenone, valerophenone, dihydrochalcone).

Materials and Methods

Catalytic runs were carried out in a gas-phase plant operating at atmospheric pressure over 1 cm³ of catalyst pellets (30-60 mesh). Reactants were mixed in the desired molar ratio and fed with a volumetric pump into a stainless-steel line to be vaporized before the catalytic bed. The LHSV and the flow of N₂ carrier were adjusted to obtain the desired molar fractions in the gas-phase maintaining a

contact time t (at reaction temperature) = 1 s. The effluent from the reactor was condensed in a cold trap filled with acetonitrile and kept at 0 °C and analyzed offline with an Agilent 5890 Series II GC instrument (internal standard = dodecane, capillary column: DB-1701, 25 m \times 530 μ m \times 1.05 μ m). The effluent from the cold trap was analyzed online by means of GC-TCD (columns: Agilent CP-Molsieve 5A capillary column, 25 m \times 530 μ m \times 50 μ m and an Agilent CP-Silica PLOT, 30 m \times 530 μ m \times 6 μ m). Ceria (CeO_2 , 193 m^2/g) was a commercial reference material (Rhodia Actalys HAS 5) and was calcined at 5 °C/min up to 400 °C for 4 h before use; zirconia (ZrO_2 , 55 m^2/g), ceria–zirconia (Ce/Zr/O , 123 m^2/g) and lanthana (La_2O_3 , 26 m^2/g) were synthesized by means of precipitation and co-precipitation, adapting a method from the literature⁶, and calcined at 5 °C/min up to 550 °C, 400 °C, and 750 °C respectively. Catalysts were characterized by means of BET, XRD, TGA, Raman and TPR.

Results and Discussion

Catalytic runs were initially carried out at 350 °C and with a contact time equal to 1 second by vaporizing the feed in N_2 carrier to obtain a total organic concentration of 2 % in the gas-phase. ZrO_2 exhibited a higher catalytic performance and stability with respect to other well-known ketonization catalysts (e.g., CeO_2 , Ce/Zr/O and La_2O_3) in the synthesis of dihydrochalcone (HC) from ethyl 3-phenyl propionate (EPP) and ethyl benzoate (EB), in analogy with previous results obtained in the coupling of methyl 2-furanoate and acetic acid towards acetyl furan⁵. A detailed investigation of the process condition showed that the main parasitic reaction, i.e. the undesired homo-ketonization of EPP towards 1,5-diphenyl propanone, could be avoided either by increasing the EB/EPP molar ratio in the feed or by increasing the reaction temperature from 350 °C to 400 °C; the latter finding could be explained by the higher reactivity of EB at higher temperature. Once optimal reaction conditions were identified for the synthesis of acetyl furan (model aryl-alkyl ketone) and dihydrochalcone (model aryl-alkyl ketone), the synthetic method was scaled up to a feed containing 20 % total organic reactants and extended to the synthesis of the valuable compounds listed in Figure 2.

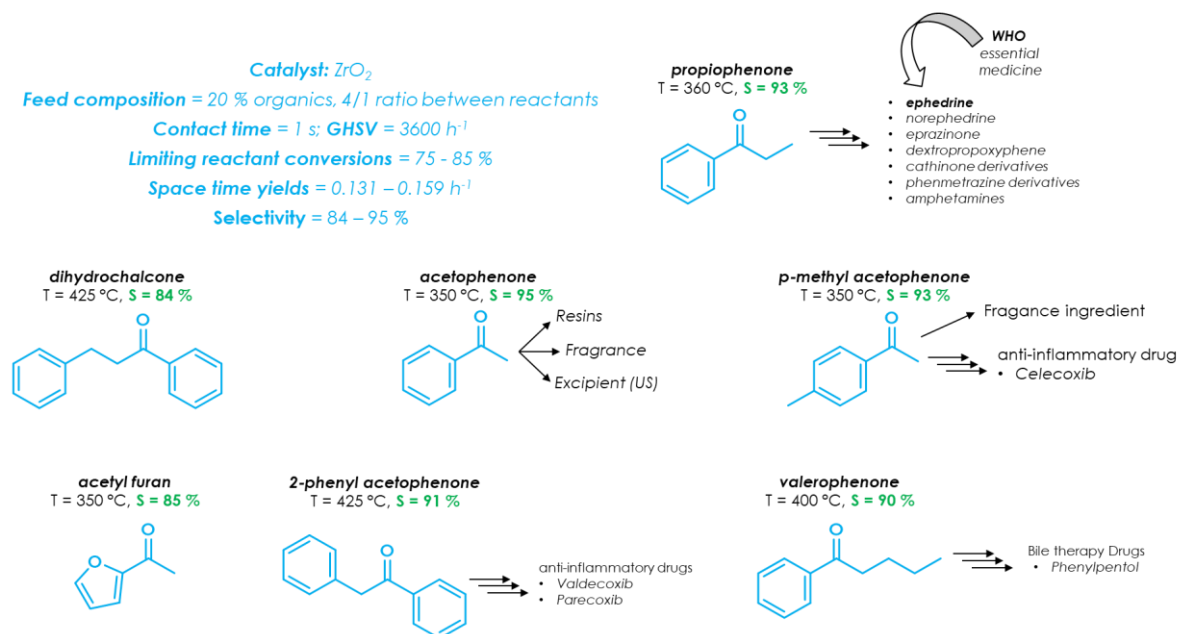


Figure 2 Substrate scope of the cross-ketonization synthetic approach.

References

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