ORGANIC
LETTERS

2007
Vol. 9, No. 21
4351−4354

Photodecarbonylation of 1,3-Dithiophenyl Propanone: Using Nanocrystals to Overcome the Filtering Effect of Highly Absorbing Trace Impurities

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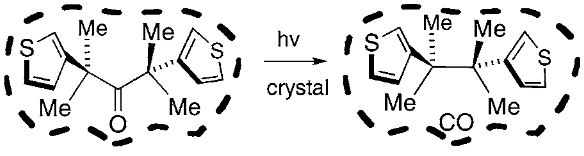
Received August 15, 2007

ABSTRACT



1 2

Irradiation of crystalline 2,4-dimethyl-2,4-di(thiophen-3-yl)pentan-3-one (1) resulted in photodecarbonylation and radical combination to give 2 with >99% selectivity. However, extended irradiation led to no more than ca. 8% conversion due to highly absorbing unidentified trace impurities that act as filters. We report here a simple procedure to improve the reaction efficiency by taking advantage of nanocrystalline suspensions prepared by the reprecipitation method, which leads to shorter reaction times and quantitative yields.

Recent developments in the design and control of reactions in crystals[1] include the use of templating strategies to preorganize reagents for bimolecular reactions,[2] ionic chiral auxiliaries to induce enantioselective reactions,[3] and chemical processes involving high-energy species to promote unimolecular reactions in a reliable manner.[4] Within the last category, we have shown that the photodecarbonylation of crystalline ketones is an efficient and promising "green chemistry" method[5] for the synthesis of structures with adjacent all-carbon quaternary centers (Scheme 1a). Numerous examples confirm that the efficiency of the solid-state reaction augments with the radical stabilizing abilities (RSE) of the α-substituents (R_1-R_6), which increase the dissociative character of the ketone α-bonds.[6−8] Using the sesquiterpenes herbertenolide[9] and α-cuparenone[10] as synthetic targets (Scheme 1b and 1c, respectively), we have shown that solid-state reactions offer significant advantages for the stereoselective synthesis of natural products.[11]

In the course of exploring the scope of the solid-state reaction with ketones having heteroaromatic substituents, we

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[1] For leading reviews, please see: (a) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433. (b) Sakamoto, M. *Chem.*—*Eur. J.* **1997**, *3*, 684. (c) Scheffer, J. R.; Garcia-Garibay, M. A.; Nalamasu, O. *Org. Photochem.* **1987**, *8*, 249.

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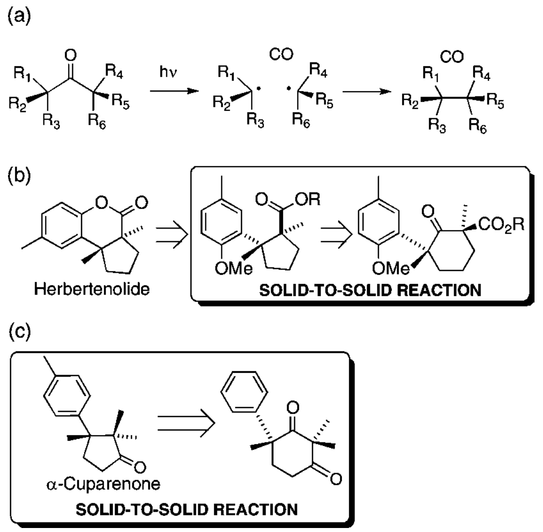
[4] (a) Garcia-Garibay, M. A.; Shin, S. H.; Sanrame, C. *Tetrahedron* **2000**, *56*, 6729. (b) Garcia-Garibay, M. A. *Acc. Chem. Res.* **2003**, *36*, 491. (c) Campos, L. M.; Garcia-Garibay, M. A. In *Reviews of Reactive Intermediate Chemistry*; Platz, M. S., Jones, M., Moss, R., Eds.; John Wiley and Sons: Hoboken, NJ, 2007.

[5] (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998. (b) Clark, J. H. *Green Chem.* **1999**, *1*, 1. (c) Hölscher, M. *Green Chem.* **2004**, *6*, G31.

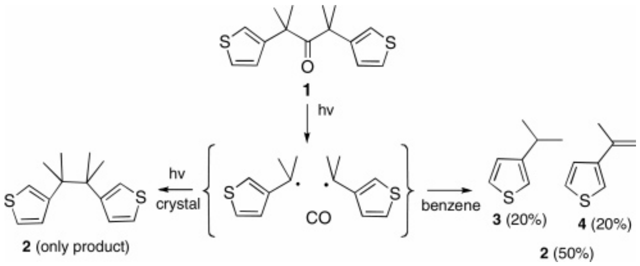
10.1021/ol702000s CCC: $37.00

Scheme 1



investigated the solid-state photochemistry of 2,4-dimethyl-2,4-di(thiophen-3-yl)pentan-3-one **1** (Scheme 2). We were encouraged by experimental[12] and computational studies[13] suggesting that the radical stabilizing ability of 3-thiophenyl is essentially the same as that of a phenyl group (RSE $\sim$ 16.5 kcal/mol). This suggests that the solid-state photochemistry of compound **1**, with two additional methyl substituents on each α-carbon, should be comparable to that of dicumyl ketone (RSE $\sim$ 21.5 kcal/mol). While this expectation was confirmed, the formation of trace amounts of impurities acting as a light filter limited the extent of conversion to impractical levels. This limitation was conveniently solved by taking advantage of samples of **1** in the form of nanocrystalline suspensions.

Scheme 2



Samples of 2,4-dimethyl-2,4-di(thiophen-3-yl)pentan-3-one **1** were obtained by methylation of 2,4-di(thiophen-3-yl)-pentan-3-one, which was obtained by dicyclohexylamide (DCC)-mediated coupling of commercial thiophen-3-ylacetic acid.[14,15] Ketone **1** was obtained as a white crystalline solid with a melting point of 80−81 °C. It was fully characterized in solution by ^{1}H and ^{13}C NMR, FTIR, and MS.[16] X-ray diffraction data from thin needles of compound **1** obtained from hexane were processed in the space group $P2_1$ with two molecules per asymmetric unit. While atomic connectivity and unit cell contents were in agreement with expectations, limited data quality and twinning prevented us from achieving a satisfactory refinement. The available data suggest a molecular structure with a conformation analogous to those previously observed with several dicumyl ketones (Figure 1),[8] with the two aromatic groups oriented above and below the plane of the carbonyl, and two of the four α-methyl groups nearly eclipsed with the C=O bond, as a result of well-documented dipole−induced dipole interactions.[17]

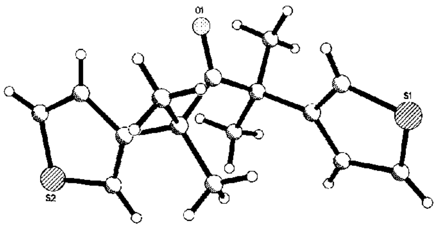


Figure 1. Molecular structure derived from single-crystal X-ray diffraction analysis for compound **1**.

UV irradiation of **1** in benzene (ca. 4 mM) with a medium-pressure Hg Hanovia lamp using Pyrex glassware as a filter (λ > 290 nm) revealed products that are consistent with the expected α-cleavage and decarbonylation followed by radical−radical reactions (Scheme 2). The previously known 2,3-dithiophenylbutane **2**[18] forms by a radical−radical combination reaction, while 3-isopropylthiophene **3** and 3-(propen-2-yl)thiophene **4** form by a radical−radical disproportionation process. The solid-state reaction was shown to be highly temperature dependent. While irradiation of powdered samples

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(6) (a) Choi, T.; Peterfy, K.; Khan, S. I.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 2477. (b) Peterfy, K.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4540. (c) Yang, Z.; Garcia-Garibay, M. A. *Org. Lett.* **2000**, *2*, 1963. (d) Yang, Z.; Ng, D.; Garcia-Garibay, M. A. *J. Org. Chem.* **2001**, *66*, 4468. (e) Campos, L. M.; Ng, D.; Yang, Z.; Dang, H.; Martinez, H. L.; Garcia-Garibay, M. A. *J. Org. Chem.* **2002**, *67*, 3749. (f) Ellison, M. E.; Ng, D.; Dang, H.; Garcia-Garibay, M. A. *Org. Lett.* **2003**, *15*, 2531. (g) Choe, T.; Khan, S. I.; Garcia-Garibay, M. A. *Photochem. Photobiol. Sci.* **2006**, *5*, 449.

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at 20 °C led to no observable product after 2 days, samples exposed to the same UV source for 24 h at ca. 45 °C gave compound **2** as the only product in ca. 5−10% yield.[19] As further light exposure did not lead to higher conversion, we analyzed the changes of crystalline **1** in more detail. Visual inspection of finely powdered crystals exposed to UV light for 2 h ($\lambda > 290$ nm, Pyrex filter) revealed a significant darkening (Figure 2). Spectroscopic analysis by diffuse reflectance UV−vis exhibited a strong diffuse absorption from ca. 300 nm to >650 nm, which is clearly responsible for the dark color.[16] ^{1}H NMR analysis of the same sample revealed only 8% conversion, with compound **2** being the only detectable product. Given that **2** only absorbs in the UV range ($\lambda < 300$ nm), we deduced that trace amounts of highly absorbing byproducts filter the incoming light and prevent excitation of **1**.[20] While attempts to accumulate and characterize the nature of the substance responsible for the dark color failed, the filtering layer could be washed away with solvents to expose a new reactive surface. We reasoned that such filtering effects should be avoidable by using crystals that are smaller than the width of the layer. To accomplish that, we decided to explore the use of nanocrystals. It has been recently shown that molecular nanocrystals offer several advantages in solid-state photochemistry, among them, the increased likelihood of single crystal-to-single crystal reactions,[21] the ease in reaction scale up to multigram quantities by using flow methods,[22] and the use of conventional transmission methods for spectroscopic applications.[23]

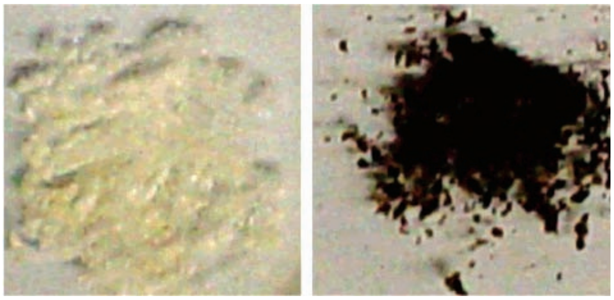

Figure 2. (Left) Polycrystalline (powder) sample of dithiophenyl ketone **1** before and (right) after 2 h of UV irradiation, with a total conversion of 7%.

Nanocrystals of **1** were conveniently prepared by the reprecipitation method,[24] and suspensions obtained in this manner have a milky-white appearance (Figure 3a) and are known to contain particles ranging in size from tens to hundreds of nanometers. The identical ATR-FTIR (attenuated total reflection) spectra of filtrated nanocrystals and macroscopic powdered samples suggested that both samples belong to the same polymorphic phase. Photochemical reactions were carried out with nanocrystalline suspensions of **1** placed in a Pyrex tube acting both as a container and as a light filter ($\lambda > 290$ nm). Samples were exposed to the output of the Hg lamp for various intervals. As expected, chemical yields analyzed by ^{1}H NMR were significantly higher than those previously observed with powdered solids. A sample irradiated for 1, 2, and 5 h led to 5, 22, and 55% conversion, respectively, with **2** formed as the only product. Satisfyingly, samples exposed to UV light for 12 h underwent a quantitative reaction to product **2** (Figure 3), which was, as in previous examples,[22] collected in pure form by simple filtration. X-ray powder diffraction (XRPD) and differential scanning calorimetric analysis (DSC) of filtered samples suggested a solid-to-solid reaction that proceeds by a reconstructive phase transition. XRPD and DSC of "as formed" nanocrystalline **2** were identical to those obtained after recrystallization.

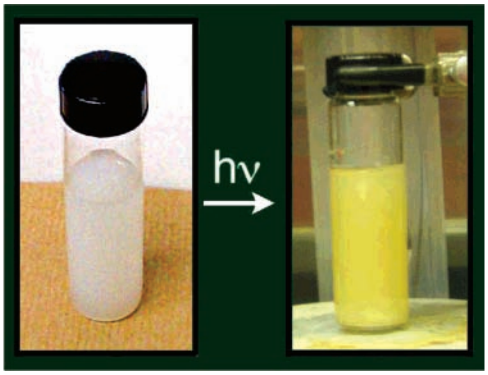

Figure 3. An aqueous suspension of nanocrystals of **1** before reaction illustrating its milky-white appearance (left), and after 100% reaction (right) showing a slight yellow discoloration.

In conclusion, the results with crystals of **1** confirm the reaction enabling abilities of the 3-thiophenyl substituent, highlight the generality of the solid-state photodecarbonylation reaction, and strongly encourage its development as an efficient "green chemistry" alternative[5] for the preparation

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[19] The temperature dependence can be attributed to the existence of energy barriers in the excited state hypersurface. Please see ref 7 and references therein.

[20] Keating, A.E.; Garcia-Garibay, M. A. In *Organic and Inorganic Photochemistry*; Ramamurthy, V., Schanze, K., Eds.; Marcel Dekker: New York, 1998; Vol. 2; pp 195−248 and references therein.

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[24] In a typical procedure, a saturated solution containing **1** (0.04g) in acetone (2 mL) was added into a rapidly stirring submicellar (2.5 mM) solution of sodium dodecyl sulfate (SDS, 7 mg) in H_2O (10 mL). The excess acetone was removed with a stream of air. The milky-white suspension was placed in a Pyrex container at a distance (∼10 cm) from a medium-pressure Hg Hanovia lamp and stirred while keeping a constant temperature inside the photolysis chamber (ca. 25 °C). The critical micelle concentration of SDS (cmc = 7−10 mM) was taken from the "Detergent Properties and Application" table from Aldrich; www.sigmaaldrich.com/img/assets/15402/Detergent_Selection_Table.pdf (accessed August 8, 2008).

of compounds with adjacent stereogenic quaternary centers in multigram quantities.[22] More importantly, we have also shown that limitations to the solid-state reaction arising from competing light absorbers can be effectively circumvented by using nanocrystalline suspensions.

Acknowledgment. This work was supported by the National Science Foundation through Grant CHE0551938.

Supporting Information Available: Syntheses and characterization of compounds **1** and **2**, photochemical procedures, ^{13}C CPMAS NMR, XPD, and DSC analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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