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Engineering Reactions in Crystalline Solids: Radical Pairs in Crystals of Dialkyl 1,3-Acetonedicarboxylates

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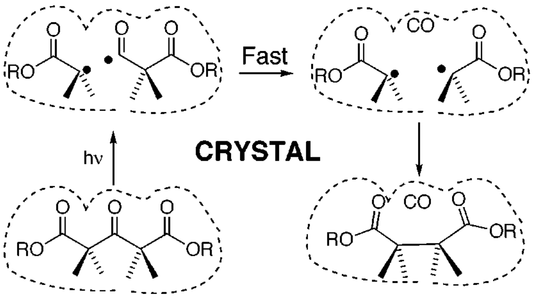
ABSTRACT



Crystalline dialkyl 1,3-acetonedicarboxylates give dialkyl succinates in high chemical yields by combination of α-carbonyl radical pairs produced by photochemical decarbonylation. It is proposed that the solid-state reaction depends on the exothermicity of two consecutive bond cleavage processes. It is also suggested that the efficiency of radical formation in the solid state is determined by the effect of substituents on bond dissociation energies and radical-stabilization abilities.

In the past few years, we have been interested in establishing strategies toward the reliable design of reactions that occur in crystalline solids. Our interest stems from the high selectivities and specificities that are frequently achieved when organic reactions are carried out in crystals[1] and from the environmental appeal of developing and exploiting chemical processes without solvents.[2] The two most serious challenges associated with the systematic analysis and exploration of organic solid-state reactivity come from its limited generality and predictability. To overcome this limitation, we have investigated the use of crystalline compounds that can generate reactive intermediates capable of undergoing bond-breaking and bond-making reactions despite severely limited motion.[3]

We have proposed that photochemical decarbonylation of crystalline ketones (Norrish type-I reaction) can generate biradicals and radical pairs with predictable efficiencies.[4] Our working hypothesis (Scheme 1) relies on the high excited-state energies of carbonyl compounds (e.g., 70−80 kcal/

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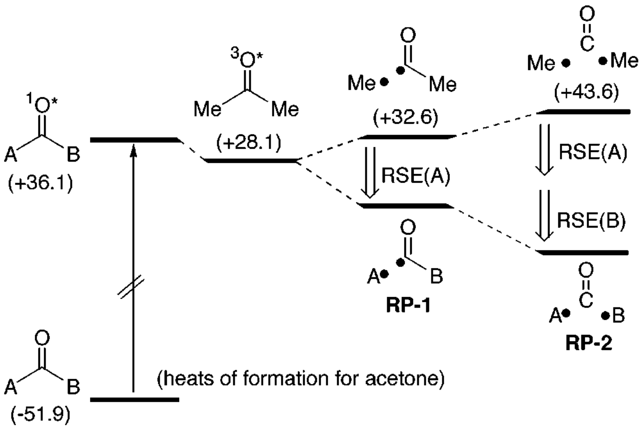
Scheme 1

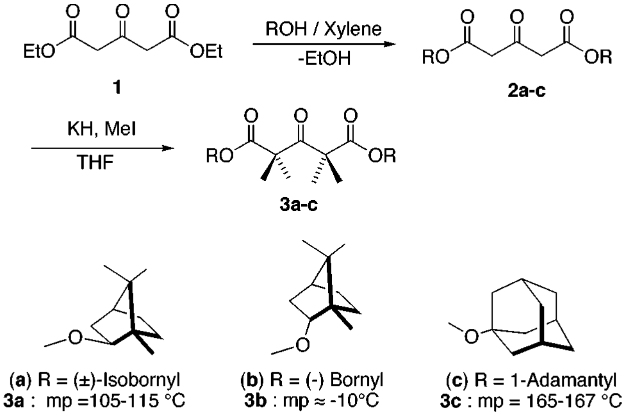


mol),[5] the availability of exothermic pathways leading to acyl−alkyl (**RP-1**) and dialkyl (**RP-2**) radical pairs, and excited-state reaction rates that can compete with other deactivation pathways. We predict that the efficiency of the solid-state reaction will depend on substituents that can lower the value of the A−CO−B bond dissociation energies by increasing the stabilities of radicals $A^{\cdot}$ and $B^{\cdot}$ [RSE(A) and RSE(B)].[6]

On the basis of thermochemical arguments and taking acetone as reference (Scheme 1), a stepwise decarbonylation reaction should become exothermic with substituents that can lower the BDE values of the α-bonds by more than ∼11 kcal/mol. This presumes that efficient decarbonylation in the solid state must be either exothermic or thermoneutral.[7] We have recently shown that α-phenyl substituents promote rapid solid-state α-cleavage and decarbonylation by formation of benzylic stabilized radicals (ca. RSE ≈ 15−20 kcal/mol) [Scheme 1, $A = B = CH_2Ph$, $A = B = C(Me)_2Ph$].[4,8] We have also shown that alkyl substituents leading to tertiary stabilized radical centers (ca. RSE ≈ 8.5 kcal/mol)[9] fail to promote the reaction in the solid state.[4b] In this Letter, we explore the solid-state reactivity of crystalline ketones having radical-stabilizing α,α′-dialkoxycarbonyl substituents (Scheme 1, $A = B = C(Me)_2CO_2R$).

Besides the radical-stabilizing effects that are needed to make the solid-state reaction possible, our interest in alkoxycarbonyl substituents comes from their potential synthetic versatility. To avoid the potential enolization of the bis-1,3-dicarbonyl system, we prepared and analyzed a set of α,α,α′,α′-tetramethyl-substituted compounds. The ketodiesters **2a**−**c** were prepared by transesterification of commercially available diethyl 1,3-acetonedicarboxylate **1** with 2.4 molar equiv of (±)-isoborneol, (−)-borneol, and 1-adamantanol in refluxing xylenes (Scheme 2).[10] The reaction proceeded in quantitative yields within 4 h by azeotropic removal of EtOH. Methylation of ketodiesters **2a**−**c** with excess KH and MeI gave the desired ketodiesters **3a**−**c** in 80−90% isolated yields.

Scheme 2



Compound **3a**, obtained as a statistical mixture of four diastereomers (meso and D,L pair), crystallized as a substitutional solid solution of diastereomers[11] with a broad melting point (105−115 °C). Compound **3b** was obtained as a single enantiomer, and it forms crystals with a very low melting point (mp < −10 °C). Compound **3c** forms large prisms which melt at 165−167 °C.

Irradiation of compounds **3a**−**c** in deoxygenated benzene at ambient temperature with a $\lambda > 305$ nm filter gave diesters **4a**−**c** along with α-methylpropionates **5a**−**c** and methacrylates **6a**−**c** (Scheme 3 and Table 1). Irradiations in the solid state gave results that depended on the crystallinity of the sample and the extent of reaction.

Scheme 3

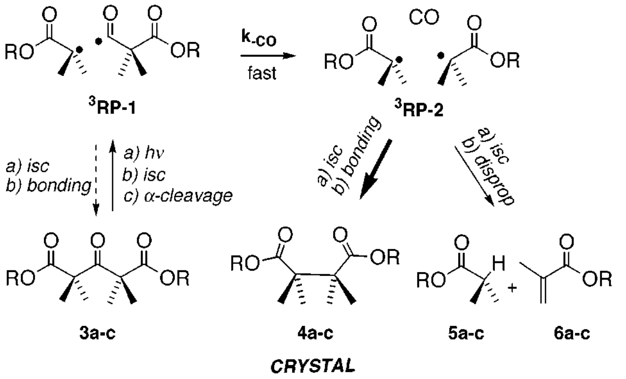


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Table 1. Product Distribution from Irradiation of Ketodiesters **3a**−**3c** in Benzene and in Crystals

ketone	reaction medium	time (h)	temp (°C)	convn (%)	**4**^{b} (%)	**5**^{b} (%)	**6**^{b} (%)
3a	benzene	4	20	100	20	45	35
	crystal	5	20	70	100	0	0
	crystal	7	20	100	70	27	3
3b	benzene	4	20	100	33	43	24
	crystal	14	−70	35	75	25	0
3c	benzene	4	20	100	24	46	29
	crystal	8	20	88	100	0	0

[a] Irradiations carried out with λ > 305 nm filter. [b] Product yields determined by gas chromatography normalized to 100%.

Reactions carried out at ambient temperature with crystals of **3a** and **3c** gave diesters **4a,c** with high selectivities and high chemical yields. In contrast, irradiation of low-melting **3b** at −70 °C gave a mixture of products in modest chemical yields.

The results in Table 1 reveal an efficient decarbonylation reaction in solution and in the solid state and are consistent with expectations that arise from the radical stabilizing abilities of tertiary α-ester groups.[9b,12] Reactions in the crystalline solid state are characterized by a very high selectivity toward radical combination. We suggest that decarbonylation in the solid state proceeds along the triplet surface. Decarbonylation of ^{3}**RP-1** to generate ^{3}**RP-2** must occur before the acyl−alkyl radical pair can intersystem cross to the singlet state and regenerate the starting ketone (Scheme 3, dashed arrow). Experiments carried out with low-melting crystals of **3b** at −70 °C proceeded inefficiently to give diester **4b** with a 75% selectivity in 35% yield. In contrast, higher melting crystals of **3a** and **3c** proceeded with 100% selectivity toward diesters **4a** and **4c** with conversion values as high as 70 and 88%, respectively.

Application of the Norrish type-I[5] reaction mechanism to ketodiesters **3a**−**c** (Scheme 3) indicates that excited-state α-cleavage to generate **RP-1** is followed by rapid decarbonylation of the acetyl radical center to generate **RP-2**. Decarbonylation in solution is likely to occur after the two radicals in **RP-1** separate to form free radicals. The fate of the α-ester tertiary free radicals in benzene is determined by subsequent radical encounters and by reaction with scavengers. Radicals encountering in the singlet state may combine to yield diester **4** or may disproportionate by hydrogen transfer to generate propionate **5** and methacrylate **6**. An experimental discrepancy between the yields of propionates **5** and methacrylates **6** may result from secondary photoreactions and free radical polymerization in the latter.

Extended irradiation at ambient temperatures resulted in crystal melting and formation of propionates **5a** and **5c**. To solve this problem, experiments are in progress to determine the phase diagram of the two-component system, which will help us determine the highest temperatures that will maintain a solid phase during the progress of the entire reaction.[13]

To our knowledge, the photochemical decarbonylation of ketodiesters has not been previously documented.[5,14]

However, on the basis of thermochemical arguments and radical delocalization data, one can expect that an ester carbonyl and two alkyl groups can stabilize a carbon radical by about 12.3 kcal/mol.[9b,15] Assuming that spin−spin interactions and conformational restrictions in the solid state do not alter the energetics by a large measure, stabilization energies of this magnitude are expected to make α-cleavage and decarbonylation reactions exothermic and nearly barrierless. The successful generation of radical pairs in crystalline ketones by using thermochemical guidelines gives a promising forecast for many other substituents. Studies with other radical stabilizing groups are currently in progress.

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Supporting Information Available: General experimental procedures and the synthesis and characterization of compounds **2**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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