Diastereoselective synthesis and spin-dependent photodecarbonylation of di(3-phenyl-2-pyrrolidinon-3-yl)ketones: synthesis of nonadjacent and adjacent stereogenic quaternary centers†

Marino J. E. Resendiz, Arunkumar Natarajan and Miguel A. Garcia-Garibay*

Received (in Bloomington, IN, USA) 2nd August 2007, Accepted 3rd November 2007
First published as an Advance Article on the web 12th November 2007
DOI: 10.1039/b711786h

A diastereoselective procedure to obtain N-para-methoxybenzyl bis-α,α’-3-(3-phenyl-2-pyrrolidinonoyl) substituted ketones with non-adjacent quaternary stereocenters, DL-2 and meso-3 was followed by a photoinduced, spin-dependent, and diastereoselective decarbonylation to give compounds DL-4 and meso-5, with adjacent all-carbon quaternary stereogenic centers.

Chemical structures with adjacent stereogenic quaternary carbon centers are relatively common in biologically active substances, including natural products and pharmaceuticals. However, despite recent advances in synthetic methodology, there are no satisfactory procedures for the preparation of this seemingly simple structural motif. The primary challenge stems from the steric impediments for six alkyl groups to converge with the precise orientation within a distance of 1.54 Å, which is the bond distance between the two adjacent carbons. To address this problem, our group has been interested in the photodecarbonylation of hexasubstituted ketones (Scheme 1). With quaternary carbon distances that are longer by 80% (ca. 2.8 Å) and easier preparation, hexasubstituted ketones are appealing synthetic intermediates. Notably, in addition to the stereocontrolled synthesis of hexasubstituted ketones, this strategy requires that the stereochemistry of the intermediate radical pair be preserved and we have shown excellent results when reactions are carried out in the crystalline solid state.

Interested in structures that occur in either meso- or DL-forms, we decided to explore the two-step procedure illustrated in Scheme 2, starting with 3-phenylpyrrolidine-2-one 1. We reasoned that deprotonation followed by reaction with a carbonyl equivalent might form the desired hexasubstituted ketones in a diastereoselective manner. We selected phenylpyrrolidinone 1 with the expectation that the resulting ketones 2 and 3 would react efficiently as a result of the radical stabilizing abilities of their α-phenyl and α-carbonyl substituents. Compound 1 also possesses the aryl, carbonyl and nitrogen functionalities that are common to many alkaloids, and should be valuable to determine the applicability of the solid-state reaction for the synthesis of complex natural products. In this communication, we report the stereoselective preparation of the DL- and meso-ketones 2 and 3 and their unexpectedly selective solution photochemistry.

Compound 1 was prepared by para-methoxybenzyl (PMB) protection of the free amide obtained by the method of Michael et al. from diethyl 2-phenylmalonate. As indicated in Scheme 2, formation of the lithium enolate of 1 with LiHMDS in THF at −78 °C followed by addition of 0.5 eq. of COCl₂ and warming up to ca. −40 °C gave the DL-pair 2 as the only detectable product in 75% isolated yield. Alternatively, reaction of the same enolate with 1,1-carbonyl diimidazolide (CDI) from −110 to −60 °C provided the meso-diastereomer 3 along with several unidentified byproducts. Reactions with COCl₂ were monitored by TLC and allowed to proceed until the starting material 1 was completely consumed, typically within 2 h. Reactions with CDI were optimized for a yield of 3 of ca. 45–50%, which gave some unreacted starting material and several unidentified products. After establishing the isomeric nature of 2 and 3 by mass spectrometry, ¹H and ¹³C NMR, their relative stereochemistry was assigned with help of single-crystal X-ray diffraction analysis of 3 which turned out to be the meso-diastereomer (Fig. 1). Notably, compound 3 adopts a non-symmetric C₁ conformation with the two phenyl substituents adopting the two sides of the plane of the carbonyl group.

The results in Scheme 2 depend strongly on the conditions indicated. Experiments carried out with NaH, NaHMDS and KH did not give the desired ketones. Only starting material and unidentified products were obtained. However, experiments with NaHMDS and 10–20 eq. of LiCl yielded the desired products,
suggesting that Li⁺ chelation is essential. There was no changes in diastereoselectivity with a large excess of LiCl using LiHMDS, suggesting that chelation of the 1,3-dicarbonyl is needed, but that lithium-mediated aggregates of the electrophile and nucleophile may not be involved. The formation of ketones 2 and 3 occurs by intermediacy of an acyl chloride in the case of COCl₂, and an acyl imidazolide in the case of CDI. Two possible reaction trajectories leading to the observed products with a lithium-chelated (S)-enantiomer of the acyl chloride (A) and acyl imidazolide (B) and approaching nucleophiles, respectively, are illustrated in Fig. 2. Structure A has the lithium enolate approaching the acyl chloride with the required si-face to form one of the enantiomers of the DL-pair. Structure B accounts for the meso-diastereoselectivity when the larger imidazolide ion is the leaving group. We speculate that adverse steric interactions between phenyl and imidazolyl groups and the preferred orientation of the enolate oxygen may cause the enolate to flip and rotate to expose the re-face. Positioning the phenyl group of the enolate in B close to the pyrrolidinone, which would have been avoided in A, would account for longer reaction times, more side products, and the lower yield of the meso diastereomer 3.

After establishing the diastereoselective synthesis of 2 and 3 we set out to investigate their photochemical reactivity in solution. Experiments were carried out in deoxygenated 0.1 M benzene solutions using a Hanovia medium pressure Hg lamp with λ > 280 nm (Pyrex filter). Two major products obtained in 60–80% were identified as the expected decarbonylation and radical–radical combination products 4 and 5 (Scheme 3). Both have a molecular ion M⁺ corresponding to the loss of CO from the starting ketones, and their ¹H and ¹³C NMR were consistent with the dynamically averaged Cₛ and C₂ symmetries of the meso- and DL-pair, respectively. The stereochimical identities of 4 and 5 were established with the help of single-crystal X-ray diffraction of DL-4 (Fig. 1, bottom).†

Remarkably, while irradiation of ketone 2 gave compounds 4 and 5 in 40 and 20% isolated yields, respectively, the yields from ketone 3 switched to 26 and 63%. Unexpectedly, they both display a ca. 2 : 1 tendency to retain the stereochemistry of the reactant in the product, requiring a mechanism with stereochimical memory. While concerted CO extrusions have been considered in the literature, there have been no conclusive examples reported. A more likely mechanism involves a singlet state α-cleavage, loss of CO, and rapid recombination of the singlet radical pair to preserve the stereochemistry of the reactant. In fact, stereospecific reactions of singlet radical pairs have been reported in the literature in the photo-Claisen reaction and decarboxylative photocyclizations.

In order to establish the stereochimical preferences of freely

Fig. 1 (Top) ORTEP diagram of ketone meso-3 (298 K) and (bottom) decarbonylation product DL-4 (100 K). Compound 4 crystallizes in a conformation with C₂ symmetry and is viewed down the twofold axis across the central C–C bond. Both structures are shown at the 30% probability level.

Fig. 2 Possible reaction trajectories showing the preferred face attack on the (S)-enantiomer of both acyl chloride and acyl imidazolide intermediates.

Scheme 3 Proposed reaction scheme to account for the spin-selective diastereoselectivity of ketone 3. A similar scheme applies to 2.
diffusing 3-phenylpyrroldinone-3-yl radicals, we explored the
triplet-sensitized photoactivity of 2 and 3 using acetone as the
solvent and sensitizer. In parallel experiments, after each reactant
was consumed, the DL-compound 4 was obtained as the major
product (ca. 50%) with only small amounts of the meso isomer
(<5%). Experiments carried out with 3 dissolved in isoprene, a
well-known triplet quencher, were completely stereospecific,
providing 5 as the only product. A kinetic scheme that accounts
for the proposed spin-selective reactivity is illustrated in Scheme 3
with meso-3 as the reactant.

As illustrated in Scheme 3, the singlet radical pair 1RP-1 preferentially formed upon direct irradiation must lose CO before
rotation within the solvent cage so that 1RP-2 may form the new σ
bond without losing the stereochemistry of the reactant. Given
that the decarbonylation of substituted phenylacetyl radicals is exothermic, the reversible formation of 1RP-1 from caged 1RP-2 and
CO is very unlikely.14 When acetone is used as the triplet
sensitizer, σ-cleavage from 3 produces the triplet radical pair 3RP-
1, which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

19.017(2) Å, c = 1.266 Mg m⁻³, F(000) = 656, Z = 4,
was consumed, the DL-compound 4 was obtained as the major
product (ca. 50%) with only small amounts of the meso isomer
(<5%). Experiments carried out with 3 dissolved in isoprene, a
well-known triplet quencher, were completely stereospecific,
providing 5 as the only product. A kinetic scheme that accounts
for the proposed spin-selective reactivity is illustrated in Scheme 3
with meso-3 as the reactant.

As illustrated in Scheme 3, the singlet radical pair 1RP-1 preferentially formed upon direct irradiation must lose CO before
rotation within the solvent cage so that 1RP-2 may form the new σ
bond without losing the stereochemistry of the reactant. Given
that the decarbonylation of substituted phenylacetyl radicals is exothermic, the reversible formation of 1RP-1 from caged 1RP-2 and
CO is very unlikely.14 When acetone is used as the triplet
sensitizer, σ-cleavage from 3 produces the triplet radical pair 3RP-
1, which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

19.017(2) Å, c = 1.266 Mg m⁻³, F(000) = 656, Z = 4,
was consumed, the DL-compound 4 was obtained as the major
product (ca. 50%) with only small amounts of the meso isomer
(<5%). Experiments carried out with 3 dissolved in isoprene, a
well-known triplet quencher, were completely stereospecific,
providing 5 as the only product. A kinetic scheme that accounts
for the proposed spin-selective reactivity is illustrated in Scheme 3
with meso-3 as the reactant.

As illustrated in Scheme 3, the singlet radical pair 1RP-1 preferentially formed upon direct irradiation must lose CO before
rotation within the solvent cage so that 1RP-2 may form the new σ
bond without losing the stereochemistry of the reactant. Given
that the decarbonylation of substituted phenylacetyl radicals is exothermic, the reversible formation of 1RP-1 from caged 1RP-2 and
CO is very unlikely.14 When acetone is used as the triplet
sensitizer, σ-cleavage from 3 produces the triplet radical pair 3RP-
1, which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.

The extent of stereoselectivity often decreases in the
triplet manifold,15 free radicals formed from either ketone
which loses CO and diffuses apart to form free radicals.