Oxazole–Carbonyl photocycloadditions: selectivity pattern and synthetic route to *erythro* α-amino, β-hydroxy ketones†

Axel G. Griesbeck,* Maren Fiege and Johann Lex

Institute of Organic Chemistry, University of Cologne, Greinstr. 4, D-50939 Köln, Germany. E-mail: griesbeck@uni-koeln.de

Received (in Liverpool, UK) 20th January 2000, Accepted 23rd February 2000

The photocycloaddition of aliphatic and aromatic aldehydes with 2,4,5-trimethyloxazole proceeds highly regio- and diastereoselectively to give bicyclic oxetanes; hydrolytic cleavage of these adducts gives selectively *erythro* α-amino, β-hydroxy methyl ketones.

The photocycloaddition of electronically excited carbonyl compounds to alkenes (Paternò–Büchi reaction, PBR) is *the* important synthetic route to oxetanes which can be subsequently transformed into polyfunctionalized products.[1] Concerning the regio- and especially diastereoselectivity of the PBR, recent experimental and theoretical work brought a remarkable increase in our understanding of triplet 1,4-biradical behaviour[2] which also improved the synthetic significance of this reaction.[3]

The regioselectivity of the PBR with unsymmetrically substituted cycloalkenes is only moderate but can be substantially increased by using cyclic enol ethers[4] and enamines,[5] respectively. The majority of these substrates show moderate simple diastereoselectivities with distinct preference for *endo*-products. This selectivity pattern is completely inverted for carbo- and heterocyclic 1,3-dienes. With respect to regio- and simple diastereoselectivity, furans have been most extensively investigated and *exo*/*endo*-selectivities of 212 : 1 (benzaldehyde addition to furan)[6] to 363 : 1 (mesitaldehyde addition to furan)[7] were determined. Similar reactivities and selectivities have been reported for pyrroles, thiophenes, thiazoles, imidazoles and pyrazoles as alkene components in Paternò–Büchi reactions.[8]

To the best of our knowledge, oxazoles have not been investigated until now. This class of heterocycles can be viewed as masked α-amino ketones or aldehydes (Fig. 1). Analogous to the furan–carbonyl photocycloaddition which equals a photo-Aldol process,[9] the oxazole-carbonyl process results in masked α-amino, β-hydroxy carbonyl compounds.

A similar concept has been evaluated already by the groups of Sekretar[10] and Scharf.[11] They used 2(3*H*)-oxazolones and 2,3-dihydrooxazoles, respectively, as alkene components and investigated the photocycloaddition with ketones and α-keto carboxylates. The simple stereoselectivity of these reactions was high, however, the regioselectivity was low with preferential formation of the 2-amino-substituted oxetanes in the case of 2,3-dihydrooxazoles. With phenylglyoxylic esters, the photocycloaddition proceeded efficiently and *endo*-phenyl (> 95%) selectively.[12]

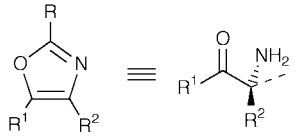
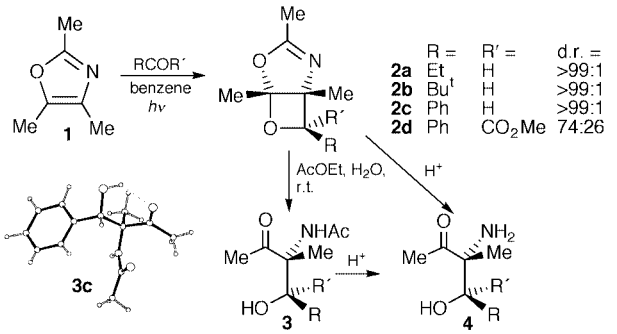


Fig. 1

† Regarded as Part 10 of the series 'Stereoselectivity of Triplet Photocycloadditions', Part 9: A. G. Griesbeck and M. Fiege, in *Molecular and Supramolecular Photochemistry*, ed. V. Ramamurthy and K. S. Schanze, Marcel Dekker, New York, 2000, vol. 6, in press.

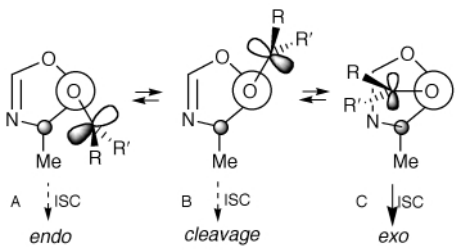
We photolyzed 2,4,5-trimethyloxazole **1** together with several aliphatic and aromatic aldehydes. In all cases, only the regioisomers **2** were formed with very high (*exo*) diastereoselectivity (> 99 : 1) in near quantitative yields (Scheme 1).



Scheme 1

Both regio- and diastereoselectivity are in accord with the rules reported by us for the carbonyl–furan photocycloaddition reaction,[6] but unusual for the oxazole derivatives mentioned above. The stereoselectivity decreased for the methyl ester of phenylglyoxylic acid: a 3 : 1 mixture of *exo*/*endo*-phenyl substituted oxetanes **2d** was isolated, however, still with high regioselectivity. This result is remarkable because not only has the stereoselectivity decreased in comparison with the results described by Scharf and coworkers,[12] but also the direction of stereocontrol was inverted. The resulting bicyclic oxetanes are thermally as well as hydrolytically labile products and were ring-opened during chromatography on silica or upon standing after several days at room temperature in moist solvents. For the benzaldehyde-derived *N*-acylated β-aminoalcohol **3c**, the primary product of this processes starting with **2c**, the *erythro* configuration was proven by means of an X-ray crystal structure determination.‡ The unprotected β-amino alcohols can be directly synthesized *via* treatment of the oxetanes **2** with trifluoroacetic acid or under milder conditions with acetic acid and conventional work-up.

From a mechanistic point of view, the stereoselectivity of the PBR with trimethyloxazole results from a combination of two factors: (1) the spin–orbit coupling controlled ISC-geometries favourable for spin inversion and transition to closed-shell products[2] and (2) the methyl-group effect which we have discovered for cyclic monoalkenes.[13] The three projections shown in Scheme 2 correspond to the three ISC-reactive



Scheme 2

DOI: 10.1039/b000578i

conformations which lead to cleavage reaction, *endo*- and *exo*-product formation, respectively.

Aldehydes (R′ = H) show strong preference for bond formation *via* structure **C** and thus give *exo* oxetanes with high stereoselectivities. For the unsubstituted furan, ketoesters (R = alkyl, aryl; R′ = CO_2R'') prefer structure **A** and give preferentially the *endo* diastereoisomers. If, however, the ring terminus of the triplet biradical is methyl substituted, additional steric interactions disfavor structure **A**. Methyl phenylglyoxylate addition to trimethyloxazole corresponds to such a case and a 3:1 *exo*/*endo* (with respect to the position of the phenyl group) mixture resulted.

In summary, we have shown that the oxazole–carbonyl photocycloaddition serves as an excellent method for the regio- and diastereoselective preparation of *erythro* β-amino alcohols from aldehydes and keto esters, respectively.

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Notes and references

‡ *Crystal data*: $C_{13}H_{17}NO_3$ (from EtOAc, mp 128–129 °C) **3c**: M = 235.28, monoclinic, space group *Cc*, a = 15.632(1), b = 9.417(1), c = 9.668(1) Å, β = 111.10(1)°; Mo-Kα radiation, 1890 reflections measured, 1055 reflections with $I > 2\sigma(I)$ R_1 = 0.51, wR_2 = 0.076. CCDC 182/1557. See http://www.rsc.org/suppdata/cc/b0/b000578i/ for crystallographic files in .cif format.

1 A. G. Griesbeck, in *Handbook of Organic Photochemistry and Photobiology*, ed. W. M. Horspool and P.-S. Song, CRC Press, Boca Raton, FL, 1995, pp. 550 and 755.
2 A. G. Griesbeck, S. Stadtmüller and H. Mauder, *Acc. Chem. Res.*, 1994, **27**, 70.
3 T. Bach, *Synthesis*, 1998, 683; *Liebigs Ann.*, 1997, 1627.
4 A. G. Griesbeck and S. Stadtmüller, *J. Am. Chem. Soc.*, 1990, **112**, 1281.
5 T. Bach, J. Schröder, T. Brandl, J. Hecht and K. Harms, *Tetrahedron*, 1998, **54**, 4507; T. Bach and J. Schröder, *J. Org. Chem.*, 1999, **64**, 1265.
6 A. G. Griesbeck, S. Buhr, M. Fiege, H. Schmickler and J. Lex, *J. Org. Chem.*, 1998, **63**, 3848.
7 A. G. Griesbeck and M. Fiege, unpublished results.
8 C. Rivas and F. Vargas, in *Handbook of Organic Photochemistry and Photobiology*, ed. W. M. Horspool and P.-S. Song, CRC Press, Boca Raton, FL, 1995, p. 536.
9 S. L. Schreiber, *Science*, 1985, **227**, 857.
10 S. Sekretar, J. Kopecky and A. Martvon, *Collect. Czech. Chem. Commun.*, 1982, **47**, 1848.
11 M. Weuthen, H.-D. Scharf and J. Runsink, *Chem. Ber.*, 1987, **120**, 1023.
12 M. Weuthen, H.-D. Scharf, J. Runsink and R. Vaßen, *Chem. Ber.*, 1988, **121**, 971.
13 A. G. Griesbeck and S. Stadtmüller, *J. Am. Chem. Soc.*, 1991, **113**, 6923.

Communication b000578i