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Rh(II)-Catalysed reactions of 2*H*-azirines with ethyl 2-acyl-2-diazoacetates. Synthesis of novel photochromic oxazines

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ABSTRACT

Photochromic non-fused 2*H*-1,4-oxazines are synthesised by a $Rh_2(OAc)_4$-catalysed reaction of 2*H*-azirines with ethyl 2-acyl-2-diazoacetates. The reaction proceeds via the formation of an azirinium ylide which undergoes ring-opening to a 2-azadiene followed by 1,6-electrocyclisation.

Photochromism is a phenomenon involving photoinduced reversible changes in the visible absorption spectrum. An important and promising class of organic photochromic materials are spirooxazines.[1] These molecules contain a fused ring-substituted 2*H*-1,4-oxazine moiety in which the C-2 atom is involved in a spiro linkage. Under UV irradiation these molecules undergo C–O bond cleavage to give merocyanine open-chain isomers, which cyclise back to the oxazine in the dark (Scheme 1).

Spirooxazines have excellent fatigue resistance and have been the subject of intense investigations as to their potential applications. These include light filters and photo-switching devices,[2] photochromic liquid crystals,[3] photochromic plastics,[4] photochromic substances used in lenses,[5] metal-complexing agents[6] and erasable optical disks.[7] The structural diversity of 2*H*-1,4-oxazines is mainly limited to *ortho*-fused derivatives (Scheme 1) because of their synthetic availability. A few simple and effective methods for their preparation from *o*-hydroxynitroso compounds, 1-amino-2-naphthols and several other compounds have been elaborated.[1a,c] A few examples of the preparation of photochromic non-spiro *ortho*-fused 2*H*-1,4-oxazines are also known.[8] The only known non-fused 2*H*-1,4-oxazine is the tricyclic 2-acetoxy-3-acetyl-substituted oxazine with a norpinane fragment which was isolated as a by-product (14%) in the reaction of the corresponding oxazin-3-one with acetyl chloride.[9] Attempts to synthesise non-fused spirooxazines by standard procedures have failed.[10]

In the context of our investigations towards the discovery of novel ylide systems as useful synthons for heterocycle design,[11] we have reacted substituted 2*H*-azirines with different carbenes and metallocarbenoids. Herein, the first method for the synthesis of non-fused 2*H*-1,4-oxazines, including spiro-derivatives based on the $Rh_2(OAc)_4$-catalysed reaction of 2*H*-azirines with 2-acyl-2-diazoacetates, is described. The ability of the products to display photochromic activity is demonstrated.

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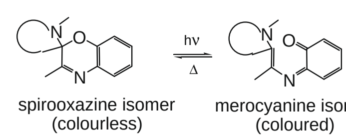
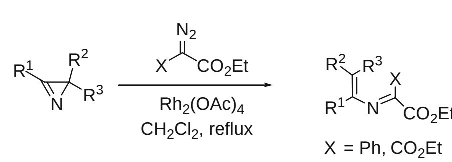
Earlier we found that 2,3-di- and 2,2,3-trisubstituted 2*H*-azirines react with dimethyl diazomalonate and methyl 2-diazo-2-phenylacetate in dichloromethane under reflux in the presence of $Rh_2(OAc)_4$ as catalyst to give substituted 2-azadienes in good yields (Scheme 2).[11f,g]

According to this protocol, slow addition, over several hours, of the diazo compound to a boiling solution of the azirine and catalyst was employed in order to avoid the competing reaction of the intermediate Rh(II)-carbenoid with the diazo compound.[11f,g]

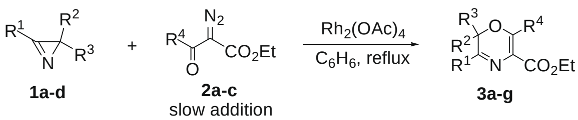
The investigation of the reactivity of the diazoketo esters under these conditions was started with the initial $Rh_2(OAc)_4$-catalysed test reaction of ethyl 2-diazoacetoacetate **2a** with 2,3-diphenyl-2*H*-azirine **1a**. It is known that diazo compound **2a** decomposes in the presence of $Rh_2(OAc)_4$ or $Cu(hfacac)_2$ at temperatures over 70 °C in benzene or fluorobenzene.[12] In fact, under the above mentioned conditions, as well as under reflux in $CHCl_3$, reaction with 2,3-diphenyl-2*H*-azirine does not occur. This process proceeds, however, in benzene at 80 °C (protocol A) and unexpectedly led



Scheme 1. Photochromism of spiro benzoxazines.



Scheme 2. The reaction of azirines with diazo esters.



Scheme 3. The reaction of azirines **1a–d** with 2-acyl-2-diazoacetates **2a–c** (protocol A).

3a,**b** and azadienes **4a,b** (Scheme 4). It was found that azadienes **4a,b** could be smoothly converted into oxazines **3a,b** by heating. To remove traces of azadiene **4a** the reaction mixture derived from azirine **1a** was heated at reflux for an additional five minutes and then purified by flash chromatography. In the case of azirine **1b**, the mixture of compounds **3b** and **4b** was purified by chromatography, and **4b** was dissolved in ethanol and heated under reflux for five hours. Azadiene **4b** cyclised quantitatively into oxazine **3b**, which crystallised from ethanol. According to this procedure oxazines **3a–d** were prepared in 73–81% yields from azirines **1a–d** and ethyl 2-diazoacetoacetate **2a**.[14] In the reaction mixture obtained from 2,3-diphenylazirine **1a** and ethyl benzoyldiazoacetate **2b**, 2-azadiene **4b** was also detected. However, in this case the modified procedure had no advantage over protocol A.

Table 1
$Rh_2(OAc)_4$-catalysed reaction of azirines **1a–d** with diazo compounds **2a–c**

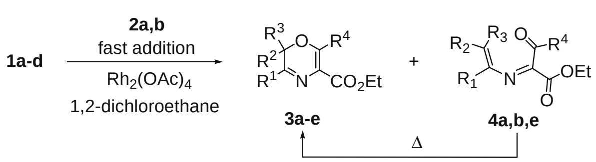
Azirine	R^1	R^2	R^3	Diazo compound	R^4	Oxazine	Yield of oxazine **3**, % protocol A/protocol B	Ratio of **3**:**4** in the reaction mixture (protocol) [a]
1a	Ph	Ph	H	**2a**	Me	**3a**	37/75	12:1 (B)
1b	Ph	2,2′-Biphenylene		**2a**	Me	**3b**	43/75	1:1 (B)
1c	Ph	H	H	**2a**	Me	**3c**	11/73	**3c** only (A, B)
1d	4-MeC_6H_4	H	H	**2a**	Me	**3d**	16/81	**3d** only (A, B)
1a	Ph	Ph	H	**2b**	Ph	**3e**	45/39	3:1 (B)
1a	Ph	Ph	H	**2c**	CF_3	**3f**	32/Traces	**3f** only (A)
1c	Ph	H	H	**2c**	CF_3	**3g**	30/Traces	**3e** only (A)

[a] Measured by ^{1}H NMR spectroscopy directly after decomposition of the last portion of diazo compound.

to the formation of 2*H*-1,4-oxazine **3a**, which was isolated in 37% yield (Scheme 3).

In this case the isomeric 2-azadiene was not observed in the reaction mixture. Analogously, oxazines **3b–g** were synthesised in 11–45% yield (Table 1, protocol A) from azirines **1a–d** and ethyl 2-acyl-2-diazoacetates **2a–c**.[13]

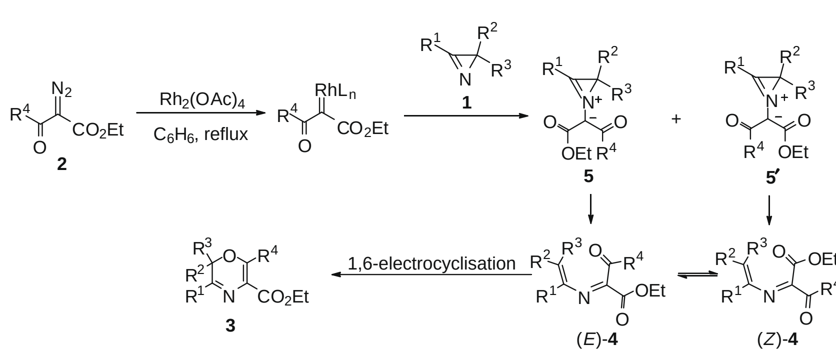
Experiments to optimise the protocol showed that the yields of oxazines **3a–d** derived from ethyl 2-diazoacetoacetate could be improved by changing the solvent from benzene to 1,2-dichloroethane as well as the rate of addition of the diazo compound: three equivalents of diazo compound were added, one equivalent was added every five minutes (protocol B).[13] According to the ^{1}H NMR data, the reaction in 1,2-dichloroethane gave smaller amounts of by-products. The decrease of product yield over prolonged reaction times was attributed to the lability of the starting azirines and oxazines formed under the reaction conditions. In the reactions of 2,3-disubstituted azirines **1a,b** with diazo compound **2a**, according to ^{1}H NMR data, two products were formed: oxazines



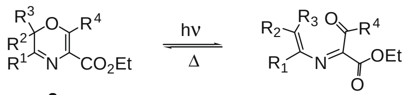
Scheme 4. The reaction of azirines **1a–d** with 2-acyl-2-diazoacetates **2a**,**b** (protocol B).

In contrast to diazo compounds **2a**,**b**, ethyl 2-diazo-4,4,4-trifluoroacetoacetate **2c** is rarely utilised in catalytic reactions. A major obstacle to its use is the number of side reactions of the diazo compound itself as well as the intermediate carbenoid.[15] The known reactions of this diazo compound usually failed to proceed in solutions of inert solvent, but provided good results when the substrate itself was used as the solvent. Nevertheless, using protocol A, we succeeded in obtaining the corresponding trifluoromethyl-substituted oxazines **3f**,**g**, albeit in poor yields. All attempts to prepare these compounds using protocol B were unsuccessful. The yields of oxazines **3a–g**, prepared according to protocols A and B, as well as the oxazine/azadiene ratio are shown in Table 1.

A mechanistic rationale for the formation of oxazines **3a–g** is shown in Scheme 5. The initial reaction involves attack of the Rh(II)-carbenoid onto the lone pair of electrons on the nitrogen of azirine **1** giving stereoisomeric azirinium ylides **5** and **5′**. Ring-opening of the three-membered ring led to isomeric azadienes (*E*)-**4** and (*Z*)-**4**. Oxazine **3** is formed via 1,6-electrocyclisation of azadiene (*E*)-**4**. None of the cyclisation products of stereoisomeric ylide (*Z*)-**5**, formed with participation of the ester carbonyl, was de-



Scheme 5. The proposed mechanism for the formation of oxazines **3** and azadienes **4**.



3 **4**

Scheme 6. Photochromic activity of oxazines **3a**–**e**.

tected in the reaction mixture. It should be noted that previously, we never observed the electrocyclisation of 2-azadienes via the oxygen of the ester group (Scheme 2).[11f,g] Apparently, the isomerisation (*Z*)-**4** → (*E*)-**4** occurs under heating. The rate of the process depends strongly upon the substitution pattern of the C=C bond in the azadiene and decreases with an increased number of aryl groups.

It was found that oxazines **3a**–**e** are photochromic compounds. Thus, according to ^{1}H NMR spectroscopy, a colourless 0.03 M solution of oxazine **3a** in C_6D_6 is converted into a yellow–orange solution of azadiene **4a** under UV irradiation (Tungsram HGOK 400 lamp) at 45 °C for 2.5 h (93% conversion) (Scheme 6). The half-life time of the reverse 'dark' cyclisation reaction of **4a** into **3a** is 80 h at 20 °C. The process of bleaching is accelerated by heating and proceeds completely after 20 min at reflux in C_6D_6.

In conclusion, the $Rh_2(OAc)_4$-catalysed reaction of 2*H*-azirines with 2-acyl-2-diazoacetates provides a convenient synthetic approach to non-fused 2*H*-1,4-oxazines. The process occurs consecutively via an unstable azirinium ylide and 2-azadiene, followed by electrocyclisation involving the keto group. 1,4-Oxazines obtained by this method are the first representatives of monocyclic 2*H*-1,4-oxazine derivatives which possess photochromic activity. Further studies on this reaction and the photochromic properties of the 2*H*-1,4-oxazines formed are currently ongoing in our laboratory.

Acknowledgement

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13. *General procedure for the preparation of oxazines* **3a**–**g**. *Protocol A*. A solution of diazo compounds **2a**–**c** (1 mmol) in anhydrous benzene (1 mL) was added dropwise over 3 h to a stirred solution of azirines **1a**–**d** (1 mmol) and $Rh_2(OAc)_4$ (5 mg) in anhydrous benzene (4 mL) at reflux under an argon atmosphere. The solvent was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (eluent: hexane–Et_2O) to give, after crystallisation from hexane–Et_2O, compounds **3a**–**g**. *Protocol B*. A solution of azirines **1a**–**d** (1 mmol) and diazo compounds **2a**, **b** (1 mmol) in anhydrous dichloroethane (4 mL) was heated to reflux under an argon atmosphere and then $Rh_2(OAc)_4$ (5 mg) was added. The mixture was stirred under reflux until nitrogen stopped flowing from the outlet (from 5 min for diazo compound **2a** to 15 min for diazo compound **2b**), after which the next two equivalents of diazo compound were added consecutively after 5 min (diazo compound **2a**) or 15 min (diazo compound **2b**) periods. The resulting mixture was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane–Et_2O followed by recrystallisation from hexane–Et_2O to give oxazines **3a**, **c**, **d** as colourless solids. In the case of the reaction of azirine **1b** with diazo compound **2a** the mixture of compounds **3b** and **4b** was separated by flash chromatography, dissolved in ethanol and heated under reflux for 5 h. Crystallisation from ethanol afforded oxazine **3b** as a colourless solid.
14. *Ethyl 6-methyl-2,3-diphenyl-2H-1,4-oxazine-5-carboxylate* (**3a**), mp 128–129 °C (from hexane–Et_2O). IR ($CHCl_3$) ν_{max}: 1725 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 1.21 (3H, t, J = 7.1 Hz, CH_3), 2.13 (3H, s, CH_3), 4.15 (2H, q, J = 7.1 Hz, CH_2), 6.13 (1H, s, H-2), 7.15–7.25 (8H, m, Ph), 7.65–7.72 (2H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4 (CH_3), 18.6 (CH_3), 60.5 (OCH_2), 72.3 (2-C), 119.8 (5-C), 126.8, 127.8, 128.6, 128.8, 129.3, 130.4, 134.9, 135.6 (Ph), 149.3 (6-C), 155.1 (3-C), 165.7 (C=O). Found: C, 74.73; H, 6.00; N, 4.44. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. *Ethyl 6-methyl-3-(4-methylphenyl)-2H-1,4-oxazine-5-carboxylate* (**3d**), mp 61–62 °C (from hexane–Et_2O); IR ($CHCl_3$) ν_{max}: 1720 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 1.41 (3H, t, J = 7.1 Hz, CH_3), 2.40 (6H, s, $2CH_3$), 4.36 (2H, q, J = 7.1 Hz, OCH_2), 4.79 (2H, s, CH_2), 7.25 (2H, d, J = 8.2 Hz, Ar), 7.77 (2H, d, J = 8.2 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4 (CH_3), 17.9 (CH_3), 21.4 (CH_3), 60.5 (OCH_2), 62.0 (CH_2), 120.5 (5-C), 126.5, 129.3, 132.2, 140.9 (Ar), 148.3 (6-C), 157.3 (3-C), 165.8 (C=O). Found: C, 69.36; H, 6.50; N, 5.31. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. *Methyl 2-[(2,3-diphenylvinyl)imino]-3-oxo-butanoate* (**4a**) ^{1}H NMR (300 MHz, $CDCl_3$): 0.96 (3H, t, J = 7.3 Hz, CH_3), 2.68 (3H, s, CH_3), 3.83 (2H, q, J = 7.3 Hz, CH_2), 6.43 (1H, s, HC=C), 7.23–7.44 (10H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): 13.5 (CH_3), 25.3 (CH_3), 61.6 (OCH_2), 117.5 (=C–H), 126.9, 127.3, 128.3, 128.4, 128.5, 129.6, 135.5, 137.2 (Ph), 145.3 (C–N), 158.7 (C=N), 162.5 (OC=O), 196.6 (CH_3C=O).
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