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Synthesis of electron-poor 4-halo-2-azabuta-1,3-dienes by Rh(II)-catalyzed diazo ester–azirine coupling. 2-Azabuta-1,3-diene-2,3-dihydroazete valence isomerism

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ABSTRACT

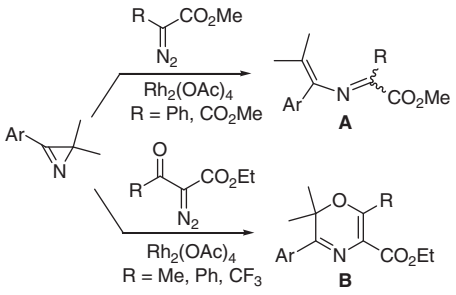
The $Rh_2(OAc)_4$-catalyzed reaction of alkyl 2-acyl-2-diazoacetates and dimethyl diazomalonate with methyl 2-bromo- and 2-chloro-3-phenyl-2*H*-azirine-2-carboxylates gives rise to electron-poor 4-halo-substituted (3*E*)-2-azabuta-1,3-dienes. Their formation proceeds with complete stereoselectivity via ring-opening of the intermediate azirinium ylide. 2-Azabuta-1,3-dienes with electron-withdrawing substituents at the 1,1,4-positions are stable compounds at room temperature, but are in equilibrium with cyclic valence isomers, 2,3-dihydroazetes, at elevated temperatures.

Due to their availability and high reactivity, 2*H*-azirines are widely used as building blocks for the synthesis of various nitrogen-containing compounds. They can act as electrophiles, nucleophiles, dienophiles, dipolarophiles, and serve as sources of nitrogen ylides.[1] One of the novel synthetic applications of these strained compounds is the Rh(II)-catalyzed azirine–diazo ester coupling to form functionalized 2-azabuta-1,3-dienes **A**,[2] (which are useful intermediates in heterocyclic synthesis[3]) and 2*H*-1,4-oxazines **B** possessing photochromic activity[4] (Scheme 1). 2-Azabuta-1,3-dienes derived from the diazo esters, methyl 2-phenyl-2-diazoacetate or dimethyl diazomalonate, are stable compounds. The reaction of aryl-substituted 2*H*-azirines with diazo keto esters furnishes unstable 1-acyl-2-azabuta-1,3-dienes which rapidly undergo 1,6-electrocyclization into 2*H*-1,4-oxazines.

2-Halo-substituted 2*H*-azirines, and particularly the most readily available alkyl 2-bromo- and 2-chloro-2*H*-azirine-2-carboxylates,[5] seemed to be attractive starting materials for the construction of halogenated 2-azabuta-1,3-dienes and 2*H*-1,4-oxazines.

In the present work the first synthesis of electron-poor 4-bromo- and 4-chloro-2-azabuta-1,3-dienes from methyl 2-halo-3-phenyl-2*H*-azirine-2-carboxylates by the $Rh_2(OAc)_4$-catalyzed reaction with alkyl 2-acyl-2-diazoacetates and dimethyl diazomalonate is described. The involvement of 4-halo-2-azabuta-1,3-dienes in the equilibrium valence isomerization into 2,3-dihydroazetes is demonstrated.

It was found that mono-, di-, and triaryl-substituted 2*H*-azirines reacted with ethyl diazoacetoacetate (**2a**) in the presence of a catalytic amount of $Rh_2(OAc)_4$ to form substituted 2*H*-1,4-oxazine **B**, as the sole product or as a mixture with functionalized 2-azabuta-1,3-diene **A**.[4] In contrast, the reaction of diazo compound **2a**



Scheme 1. Rh(II)-catalyzed reactions of aryl-substituted 2*H*-azirines with diazo esters and diazo keto esters.

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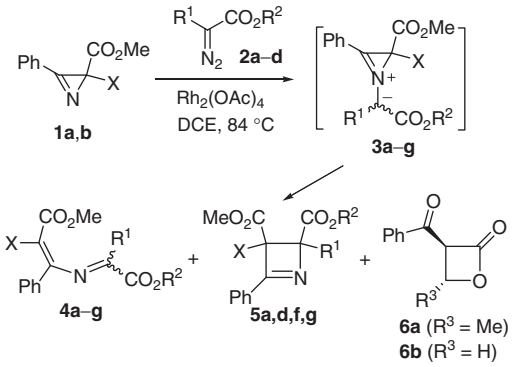


Scheme 2. The reaction of azirines **1a**,**b** with diazo compounds **2a**–**d** (4–6 equiv) in the presence of $Rh_2(OAc)_4$) (5 mol %) over 20–90 min.

Table 1
$Rh_2(OAc)_4$-catalyzed reactions of azirines **1a**,**b** with diazo compounds **2a**–**d**

Azirine	X	Diazo compound	R^1	R^2	Yield of **4** (%)	Yield of **5** (%)
1a	Br	**2a**	Ac	Et	43 (**4a**)	22 (**5a**)[a]
1a	Br	**2b**	Bz	Et	35 (**4b**)[b]	0 (**5b**)
1a	Br	**2c**	Bz	Me	52 (**4c**)[c]	0 (**5c**)
1b	Cl	**2a**	Ac	Et	56 (**4d**)	10 (**5d**)[a]
1b	Cl	**2b**	Bz	Et	30 (**4e**)[b]	0 (**5e**)
1a	Br	**2d**	CO_2Me	Me	32 (**4f**)[d]	25 (**5f**)[d]
1b	Cl	**2d**	CO_2Me	Me	60 (**4g**)	17 (**5g**)

[a] Diastereomeric ratio = 1:1.
[b] 3-Benzoyl-4-methyloxetan-2-one (**6a**) was formed as a by-product (**4b**,**e**/**6a** ratio as measured by ^{1}H NMR spectroscopy is 1:2).
[c] 3-Benzoyloxetan-2-one (**6b**) was formed as a by-product (**4c**/**6b** ratio as measured by ^{1}H NMR spectroscopy is 3:1).
[d] The reaction time is 30 min.

with methyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate (**1a**) in the presence of 5 mol % of $Rh_2(OAc)_4$ in 1,2-dichloroethane (DCE) under reflux gave three products: 2-azabuta-1,3-diene **4a** and a 1:1 mixture of two diastereomeric 2,3-dihydroazetes[6] **5a** (Scheme 2, Table 1). No traces of the corresponding 2-bromo-2*H*-1,4-oxazine were found in the reaction mixture. Azadiene **4a** was separated from the non-separable mixture of *cis*, *trans*-**5a** by column chromatography.[7]

A 1:2 ratio of 2-azadiene **4b** and *trans*-3-benzoyl-4-methyloxetan-2-one (**6a**) was obtained from the reaction of azirine **1a** with ethyl 2-benzoyl-2-diazoacetate (**2b**). The oxetanone **6a** is a known product of intramolecular insertion of a rhodium carbenoid (generated from ethyl benzoyldiazoacetate) into a C–H bond of the methylene group.[8,9] The undesirable product of carbenoid CH-insertion, 3-benzoyloxetan-2-one (**6b**), was also formed, but in substantially less amounts, when the methyl ester of benzoyldiazoacetic acid **2c** in the presence of $Rh_2(OAc)_4$ was reacted with azirine **1a** (azadiene/oxetanone ratio = 3:1). For that reason the dimethyl ester **4c** was obtained in higher yield than the methyl, ethyl ester **4b**. The formation of azadienes in these reactions proceeds with complete stereoselectivity to give only (3*E*)-2-azabuta-1,3-dienes.

Changing from bromine to chlorine in the starting azirines led to a decrease in the yield of dihydroazetes, but did not affect the yields of azadienes or the selectivity of the reaction: complete *E*-stereoselectivity of chloroazadiene **4d**,**e** formation and the non-stereoselective formation of chloroazetine **5d** were observed. No traces of dihydroazetes **5b**,**c**,**e** were detected in the reactions of benzoyldiazoacetates **2b**,**c** with azirines **1a**,**b**.

The formation of significant amounts of dihydroazetes was observed in the reaction of azirines **1a**,**b** with dimethyl diazomalonate (**2d**) under the same reaction conditions (Table 1). It was found that the product yields depended dramatically on the reaction time. Thus, the addition of diazo compound **2d** to a solution of azirine **1a** and $Rh_2(OAc)_4$ in DCE over 30 min under reflux provided azadiene **4f** and dihydroazete **5f** in 32% and 25% yields, respectively, while after 80 min of reaction the yields were 14% and 32%.

Compounds **4a**–**g** and **5a**,**d**,**f**,**g** were fully characterized using standard spectral methods.[10] The structure of dihydroazete **5f** and the *E* configuration of the C=C bond in azadiene **4b** were confirmed by X-ray analysis (Fig. 1).[11,12] The C=N bond of compound **4b** in the crystal form had *Z* configuration, whereas most probably in solution it exists as a mixture of *Z*- and *E*-isomers, which are under rapid equilibrium. This conclusion follows from the magnetic equivalence of methoxy protons and carbonyl carbons in the ^{1}H and ^{13}C NMR spectra of compounds **4f**,**g**, as well as from the low values of the activation barriers for *N*-inversion for the related C=N-containing systems.[13] The *Z*-configuration of molecule **4b** in the crystal may be caused by Br...O3 halogen bonds (Br...O 3.052(1) Å) with the oxygen atom of the carboxylate group in the *Z*-position. These pairs of interactions link molecules **4b** as centro-symmetrical dimers in the crystal state.

The reaction mechanism (Scheme 2) involving formation of ylide intermediate **3** is in good agreement with the observed stereoselectivity of the ring-opening of the three-membered ring.

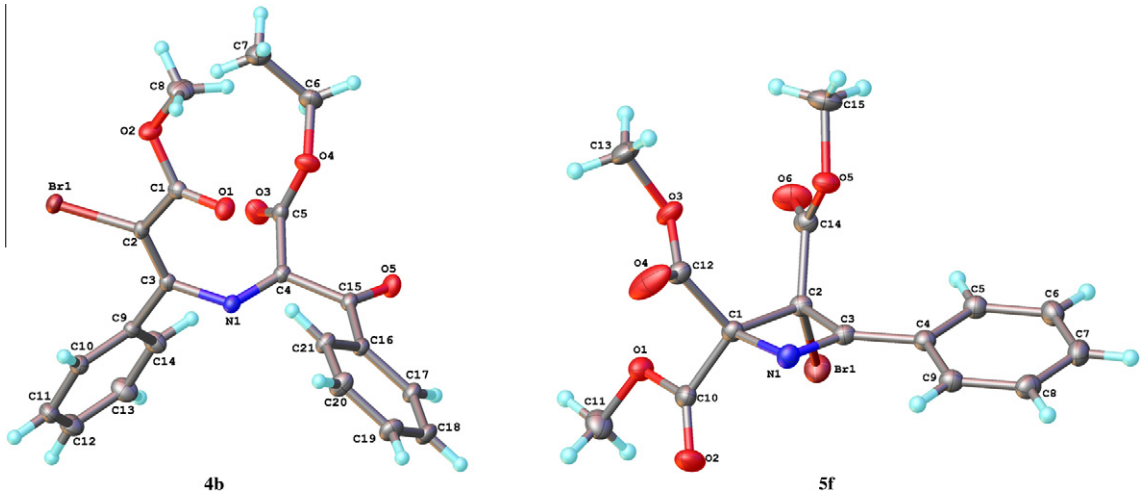
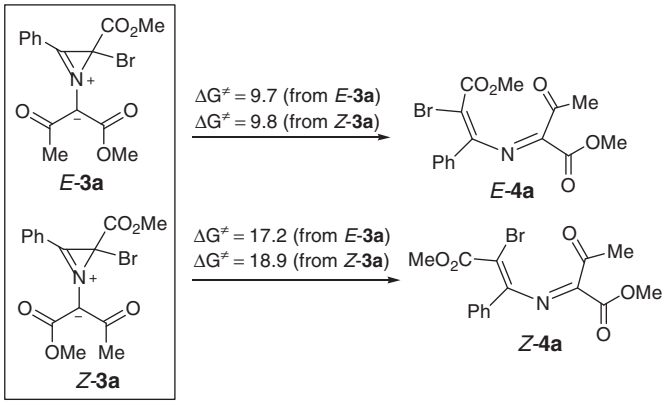


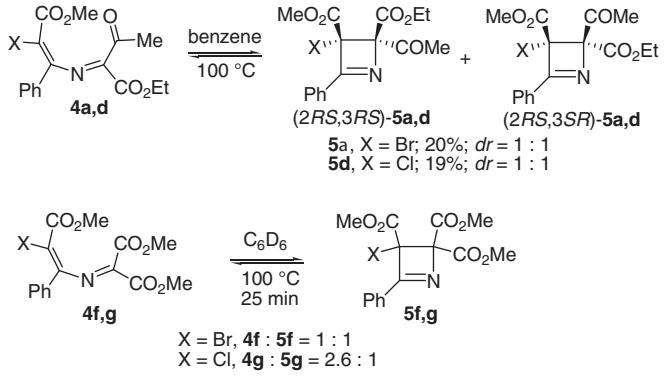
Figure 1. X-ray structures of compounds **4b** and **5f**.



Scheme 3. Activation free energies for the ring-opening of isomeric azirinium ylides *E*/*Z*-**3a** to give 2-azabuta-1,3-diene isomers **4a** (kcal/mol).

Quantum-chemical calculations (DFT B3LYP/6-31G(d)/LANL2DZ)[14] for the isomerization of *E*-**3a** and *Z*-**3a** ylides to azadiene **4a** predict a big difference for the activation barriers ($\Delta\Delta G^{\neq}$ = 7.5–9.1 kcal/mol) for the three-membered ring-opening of ylides **3** leading to (3*E*)- and (3*Z*)-2-azabuta-1,3-dienes **4** in favor of the former (Scheme 3). In fact, according to ^{1}H NMR spectroscopy and TLC data, no traces of the (3*Z*)-isomers of 2-azabuta-1,3-dienes **4a**–**e** were observed in the reaction mixtures.

The only example of carbenoid-mediated azirine–2,3-dihydroazete transformation was observed in the $Rh_2(OAc)_4$-catalyzed reaction of 2,3-diphenyl-2*H*-azirine with dimethyl diazomalonate.[2b] No immediate precursor of the 2,3-dihydroazete was observed in this reaction and the mechanism of its formation had remained unclear. The most reasonable sequence leading to the 2,3-dihydroazete system is a domino reaction involving consecutive formation of a rhodium carbenoid, an azirinium ylide **3**, and a 2-azabuta-1,3-diene (Scheme 2) followed by 1,4-cyclization of the latter, although to the best of our knowledge, this reaction is unknown in the literature. The reaction of azirine **1a** with diazo compound **2a** was shown to be the first to provide both 2,3-dihydroazete **5a** and its probable precursor, 2-azabuta-1,3-diene **4a**. It was found, that heating a benzene solution of azadiene **4a** or **4d** in a vial with a screw cap at 100 °C for 20 min led to a complex mixture of products including two diastereomeric dihydroazetes **5a**/**5d**. The latter were formed in the same 1:1 ratio as in the reaction of **1a**,**b** with **2a** (Scheme 4). They were isolated by chromatography in 19–20% overall yield. The 1,4-electrocyclization of **4a**,**d** into **5a**,**d** was found to be reversible: an azadiene **4a**,**d** impurity was detected by ^{1}H NMR spectroscopy after prolonged storage of a solution of the originally pure diastereomeric mixture **5a**,**d** at room temperature.



Scheme 4. Valence isomerism of 2-azadienes **4a**,**d**,**f**,**g**.

In contrast to compounds **4a**,**d**, azadienes **4f**,**g**, derived from dimethyl diazomalonate, smoothly undergo reversible 1,4-cyclization to give dihydroazetes **5f**,**g**, as the only products (Scheme 4). The equilibrium was attained in 25 min when a solution of the bromo-substituted azadiene **4f** in C_6D_6 was heated in a sealed tube at 100 °C giving a mixture **4f**/**5f** in a 1:1 ratio. A change from bromine to chlorine in azadiene **4** led to stabilization of the open-chain valence isomer **4g**, which is present in the equilibrium mixture in 2.6 times higher quantity than the corresponding cyclic isomer **5g**.

In summary, we have reported the first example of the reaction of 2-halo-substituted 2*H*-azirines with a rhodium carbenoid, generated from 2-acyl-2-diazoacetates and dimethyl diazomalonate, leading to electron-poor 4-bromo- and 4-chloro-2-azabuta-1,3-dienes. The complete stereoselectivity of the reaction is in accordance with a mechanism involving the formation of an intermediate azirinium ylide and predicts the preferential formation of an azadiene with *E* configuration of the C=C bond. It was established that 2-azabuta-1,3-dienes with electron-withdrawing substituents at the 1,1,4-positions were stable compounds at room temperature, but existed in solution at elevated temperatures in equilibrium with cyclic valence isomers, 2,3-dihydroazetes.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.063. These data include MOL files and InChiKeys of the most important compounds described in this article.

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7. *General procedure for the preparation of azadienes **4a–g** and dihydroazetes **5a,d,f,g**.* A solution of diazo compound **2a** (2.36 mmol) in anhydrous DCE (1.5 mL) or **2b**,**c** (3.54 mmol) in anhydrous DCE (3 mL), or **2d** (1.18 mmol) in anhydrous DCE (1 ml) was added dropwise to a stirred solution of azirine **1a**,**b** (0.59 mmol) and $Rh_2(OAc)_4$ (15 mg) in anhydrous DCE (1 mL) at reflux under

an argon atmosphere. The solvent was evaporated in vacuum and the residue was purified by column chromatography on silica gel (eluent: benzene/EtOAc from 300:1 to 100:1) followed by crystallization of the resulting solid, to give compounds **4a**–**g** and **5a**,**d**,**f**,**g**.

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10. *Methyl (2E)-2-bromo-3-{[1-(ethoxycarbonyl)-2-oxo-2-phenyl-ethylidene]amino}-3-phenylprop-2-enoate (**4b**)*, yellow solid, mp 84–86 °C (from hexane to Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, t, J = 7.3 Hz, CH_3), 3.84 (3H, CH_3O), 4.34 (2H, q, J = 7.3 Hz, CH_2O), 7.37–7.40 (3H, m, Ph), 7.47–7.52 (4H, m, Ph), 7.62–7.67 (1H, m, Ph), 8.07–7.13 (2H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 53.0 (CH_3), 62.8 (CH_2), 92.2 (=CBr), 128.1, 128.6, 128.8, 129.7, 130.3, 133.7, 134.4, 136.4 (Ph), 154.2, 157.3, 159.3, 163.5, 189.2 (C=N, C=O). HRMS-ESI calcd for $C_{21}H_{18}NO_5Br$ $[M+H]^+$ 444.0441, found 444.0437. Crystal data: $C_{21}H_{18}NO_5Br$, M = 444.27, triclinic, space group P-1, a = 8.9820(2), b = 9.7558(2), c = 11.4619(3) Å, α = 95.76(1), β = 96.53(1), γ = 103.63(1)°, U = 963.81(4) Å^3, F(000) = 452, Z = 2, D_c = 1.531 mg m^{-3}, μ = 2.165 mm^{-1} (Mo–Kα, λ = 0.71073 Å), T = 120(1) K. Dimethyl 2-[(*E*)-2-bromo-3-methoxy-3-oxo-1-phenylprop-1-enylimino]malonate (**4f**), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (3H, s, CH_3O), 3.90 (6H, s, $2CH_3O$), 7.41–7.43 (3H, m, Ph), 7.54–7.58 (2H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.0 ($2CH_3O$), 53.3 (CH_3O), 92.7 (=C–Br), 128.2, 128.6, 129.8, 135.9 (Ph), 148.8 (C=N), 156.9 (=CN), 163.2 (C=O). HRMS-ESI calcd for $C_{15}H_{14}BrNO_6$ $[M+Na]^+$ 405.9897, found 405.9897. Trimethyl 3-bromo-4-phenyl-2,3-dihydroazete-2,2,3-tricarboxylate (**5f**), mp 103–104 °C (from hexane to CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (3H, s, CH_3O), 3.86 (3H, s, CH_3O), 3.94 (3H, s, CH_3O), 7.47–7.52 (2H, m, Ph), 7.57–7.62 (1H, m, Ph), 7.94–7.97 (2H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.4 (CH_3O), 53.7 (CH_3O), 53.9 (3-C), 54.0 (CH_3), 79.3 (2-C), 127.6, 127.7, 128.7, 133.4 (Ph), 164.8, 165.1, 165.2 (C=O), 185.0 (4-C). Elem. Anal. Found: C, 46.92; H, 3.42; N, 3.73. Calcd for $C_{15}H_{14}BrNO_6$: C, 46.89; H, 3.67; N, 3.65. Crystal data: $C_{15}H_{14}BrNO_6$, M = 384.18, triclinic, space group P-1, a = 8.3126(2), b = 9.9057(3), c = 10.3924(3) Å, α = 88.56(1), β = 67.44(1), γ = 86.20(1)°, U = 788.49(4) Å^3, F(000) = 388, Z = 2, D_c = 1.618 mg m^{-3}, μ = 2.637 mm^{-1} (Mo–Kα, λ = 0.71073 Å), T = 120(1) K.
11. Crystallographic data for the structure **4b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 889607. Copies of these data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).
12. Crystallographic data for the structure **5f** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 889608. Copies of these data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).
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