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A simple approach to azirines containing an aldehyde functionality and their stabilization as palladium(II) complexes

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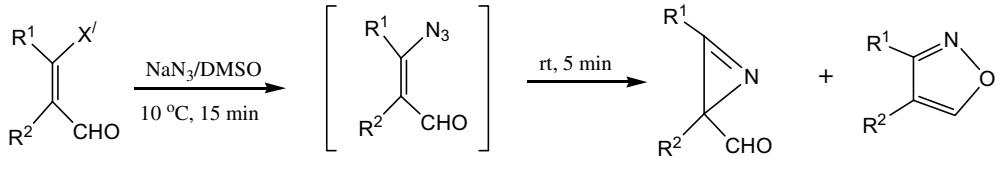
Abstract—A simple and useful method for the synthesis of azirines containing an aldehyde functionality, from open chain bromo/chloro-aldehydes at room temperature and their stabilization as palladium(II) complexes are reported.

1. Introduction

Nitrogen-containing heterocycles are versatile structures, which often occur in natural products[1–3] and frequently show biological activity.[4,5] Among them, azirines are highly reactive three-membered unsaturated strained heterocycles.[6,7] Each of the three bonds of the azirine can be cleaved depending on the experimental conditions used and hence azirines have been used for the preparation of a wide range of polyfunctional acyclic and cyclic nitrogen-containing compounds.[8,9] This small ring can act as a dienophile or as a dipolarophile and can also function as an electrophile or nucleophile.[4,6] Azirines are thermally unstable[10] and decompose even at ambient temperature.[11] They are stabilized by forming complexes with transition metals.[12] It was reported that, compared to free azirines, their palladium complexes exhibit an unusually high stability towards air, moisture and UV light.[13]

The most common and efficient route for the preparation of azirines involves the photolysis or thermolysis of vinyl azides, through a vinyl nitrene intermediate.[14] In this paper, we describe a simple route to 3-substituted-2-formyl-azirines **3** and **7** from acyclic vinyl bromo/chloro-aldehydes **1** and **5**. Padwa et al. synthesized azirines such as **3** by the addition of iodine azide to the dimethyl acetal of cinnamaldehyde followed by dehydrohalogenation, thermolysis and hydrolysis.[15]

In our synthesis, the acyclic bromo/chloro-aldehydes **1**[16] were reacted with sodium azide in DMSO at 10 °C to give the corresponding non-isolable 3-azido-aldehydes **2**, which at room temperature underwent spontaneous denitrogenation and ring closure to 2-formyl-azirines **3** as the major products presumably via the corresponding vinyl nitrenes[17] (Scheme 1 and Table 1). We also obtained isoxazoles **4** although in very low yields.



1 **2** **3** **4**

Scheme 1.

Keywords: Bromo/chloro-aldehyde; Vinyl nitrene; Azirines; Palladium complex.
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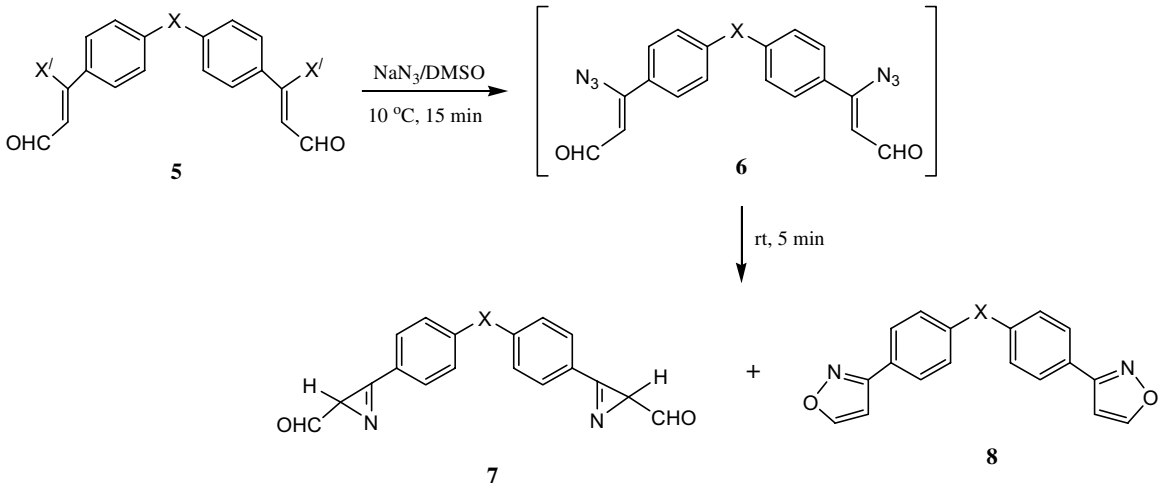
Table 1. Reaction of bromo/chloro-aldehydes **1a–f** with NaN_3 in DMSO

Entry	Substrates	Products	Yield (%) (azirine, isoxazole)
1	**1a** (R^1 = Ph, R^2 = H, X′ = Cl)	**3a**, **4a**	65, 8
2	**1b** (R^1 = naphthyl, R^2 = H, X′ = Cl)	**3b**, **4b**	63, 7
3	**1c** (R^1 = Ph, R^2 = Ph, X′ = Cl)	**3c**, **4c**	60, 6
4	**1d** (R^1 = Ph, R^2 = H, X′ = Br)	**3a**, **4a**	68, 8
5	**1e** (R^1 = naphthyl, R^2 = H, X′ = Br)	**3b**, **4b**	64, 6
6	**1f** (R^1 = Ph, R^2 = Ph, X′ = Br)	**3c**, **4c**	61, 7



Scheme 2.

Table 2. Reaction of bis-bromo/chloro-aldehydes **5a–f** with NaN_3 in DMSO

Entry	Substrates	Products	Yield (%) (azirine, isoxazole)
1	**5a** (X = CH_2, X′ = Cl)	**7a**, **8a**	60, 8
2	**5b** (X = O, X′ = Cl)	**7b**, **8b**	57, 7
3	**5c** (X = S, X′ = Cl)	**7c**, **8c**	58, 6
4	**5d** (X = CH_2, X′ = Br)	**7a**, **8a**	47, 8
5	**5e** (X = O, X′ = Br)	**7b**, **8b**	42, 7
6	**5f** (X = S, X′ = Br)	**7c**, **8c**	44, 6

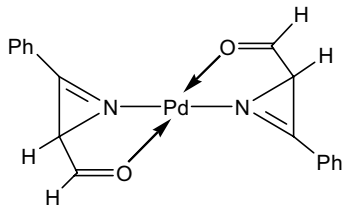


Figure 1. Palladium complex of **3a**.

Bis-bromo/chloro-aldehydes **5**[18] also underwent reaction in analogous fashion, that is, giving mainly 2*H*-azirines **7** with minor amounts of isoxazoles **8** (Scheme 2 and Table 2).

For the detection of unstable azido-aldehydes **2** and **6** we performed the reaction of chloroaldehyde **1** and **5** with sodium azide in an NMR tube using DMSO-d_6 as solvent.[19] A UV study showed a prominent isosbestic point, which indicated that the reaction proceeds through intermediate, presumably an azide or a vinyl nitrene. There are several reports about photolyses and pyrolyses of vinyl azides where the nitrene intermediate could not be detected.[20,21]

Since azirines are very unstable, we tried to stabilize our products by forming complexes with $Pd(PhCN)_2Cl_2$. It had been reported that the lone pair of an azirine nitrogen coordinates with palladium resulting in a 2:1 azirine–palladium complex with a *trans* configuration.[13] However, our azirines **3** formed complexes with palladium in a 2:1 ratio, which were different from the usual Pd–azirine complexes. Here, the lone pairs of both the azirine nitrogens and aldehyde oxygens were involved in the coordination (Fig. 1).

A most exciting result was obtained when bis-azirines **7** were reacted with $Pd(PhCN)_2Cl_2$. In this case, both azirine nitrogens and an aldehyde oxygen from either ring were involved in the coordination forming a 1:1 complex (Fig. 2) in order to attain *trans* geometry. To the best of our knowledge this is the first example of a 1:1 azirine–Pd complex. The ^1H NMR and mass spectra were consistent with the assigned structures (Figs. 1 and 2).[22]

Typical experimental procedure for syntheses of 2-formyl-azirines: To an ice-cold solution of sodium azide (2.5 mmol) in DMSO (15 ml), a solution of bromo- or chloroaldehyde **1** (1 mmol) dissolved in DMSO was

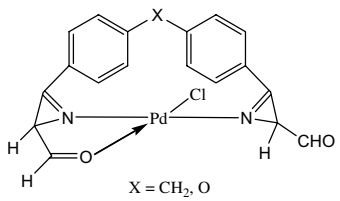


Figure 2. Palladium complexes of **7a** and **7b**.

added dropwise. The mixture was stirred for 15 min at 10 °C and then for 5 min at rt (25–30 °C). Then, the reaction mixture was decomposed with water and the aqueous portion was extracted with DCM. Removal of the solvent under reduced pressure followed by purification by preparative TLC [silica gel GF-254, hexane–ethyl acetate (7:1) as eluent] gave 2-formyl-azirines **3** (60–68%) and the isoxazoles **4** (6–8%) as the only isolable products. 2*H*-azirines **7** were prepared in a similar manner.

Physical and spectral data for **3b**: Yellow viscous liquid, IR (KBr) ν_{max}: 1771, 1706, 1279, 1110, 819 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.92 (d, 1H, $J = 6.6$ Hz C*H*=O), 7.86–7.97 (m, 4H), 7.53–7.63 (m, 3H), 2.89 (d, 1H, $J = 2.6$ Hz for azirine-H); MS (ES^+): *m*/*z* 196 [M^++H], 167 [M^+−CO]; Elemental analysis calcd for $C_{13}H_9NO$: C 80.07, H 4.65, N 7.18, found C 79.98, H 4.65, N 7.0. For **4b**: ^1H NMR (200 MHz, $CDCl_3$): δ 8.50 (d, 1H, $J = 1.5$ Hz), 8.27 (1H, s), 7.87–7.97 (4H, m), 7.51–7.59 (2H, m), 6.80 (d, 1H, $J = 1.5$ Hz).

Physical and spectral data for **7a**: Pale yellow viscous liquid, IR (KBr) ν_{max}: 1738, 1618 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.95 (d, 2H, $J = 6.4$ Hz C*H*=O), 7.88 (d, 4H, $J = 8.1$ Hz), 7.44 (d, 4H, $J = 8.1$ Hz), 4.21 (s, 2H), 2.87 (d, 2H, $J = 6.4$ Hz azirine-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 200.00$, 158.93, 146.70, 130.63, 129.34, 42.19, 38.95, 29.67; MS (FAB): *m*/*z* 303 [M^++H]; Elemental analysis calcd for $C_{19}H_{14}N_2O_2$: C 75.48, H 4.67, N 9.27; found C 75.35, H 4.71, N 9.17. For **8a**: ^1H NMR (200 MHz, $CDCl_3$): δ 8.43 (d, 2H, $J = 1.5$ Hz), 7.75 (d, 4H, $J = 10.3$ Hz), 6.62 (d, 2H, $J = 1.5$ Hz), 4.07 (s, 2H).

Typical procedure for the formation of azirine–palladium complexes: Two equivalents of azirine **3a** or one equivalent of azirine **7a** was added to a suspension of $Pd(PhCN)_2Cl_2$ (1.0 mmol) in benzene (10 ml), the mixture was stirred for 10 min, then ether (20 ml) was added. The product was collected by filtration and washed with ether to give the pure corresponding palladium complex.

Physical and spectral data for the palladium complex of **3a**: Yellow powdered solid, mp: darkened at 165 °C , IR (KBr) ν_{max}: 1780, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.86 (d, 1H, $J = 2.9$ Hz), 8.83 (d, 1H, 2.7 Hz), 7.91 (d, 4H, $J = 7.2$ Hz), 6.42–7.14 (m, 6H), 2.55 (d, 2H, $J = 6.0$ Hz); MS (ES^+): *m*/*z* 395.28, 396.01, 398.28 [$2M^+$+Pd]; Elemental analysis calcd for $C_{18}H_{14}N_2O_2Pd$: C 54.49, H 3.56, N 7.06; found C 54.42, H 3.61, N 6.98.

An EPR study of this complex revealed that it was a diamagnetic species and so it should adopt a square planner structure. If we consider the geometry of the complex as *cis* then the two aldehyde groups should be identical and should appear as a doublet in the NMR spectra. However as we observed two sets of resonances for the aldehyde protons, the complex must adopt a *trans* geometry.

Physical and spectral data for the palladium complex of **7a**: Brownish yellow powdery solid, mp: darkened at 185 °C , IR (KBr) ν_{max}: 1770, 1740, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.97 (d, 1H, $J = 6.2$ Hz), 8.95 (d, 1H, 6.6 Hz), 7.94 (d, 2H, $J = 8.6$ Hz), 7.70 (d, 2H, $J = 8.6$), 7.43–7.07 (m, 6H), 2.89 (d, 1H, $J = 6.2$ Hz), 2.87 (d, 1H, $J = 6.5$); MS (ES^+): *m*/*z* 441.84, 443.84, 445.84 [M^++PdCl]; Elemental analysis calcd for $C_{19}H_{14}N_2O_2ClPd$: C 51.36, H 3.15, N 6.31; found C 51.31, H 3.20, N 6.28.

2. Conclusion

This work reports that 3-substituted 2-formyl-azirines can be obtained in moderate yields from open chain vinyl bromo/chloro-aldehydes at room temperature and consequently forming complexes with palladium can stabilize these products. To the best of our knowledge, compounds **7a** and **7b** constitute the first examples of 1:1 complexes of bis-2-formyl azirines with palladium(II) salts.

Acknowledgements

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References and notes

1. Stapley, E. O.; Hendlin, D.; Jackson, M.; Miller, A. K. *J. Antibiot.* **1971**, *24*, 42.
2. Miller, T. W.; Tristram, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48.
3. Salomon, C. E.; Williams, D. H.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1463.
4. Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, p 47.
5. Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Synthesis, Patents, Applications*, 3rd ed.; Thieme: Wurtsburg, Germany, 1999.
6. Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; de los Santos, J. M. *Org. Prep. Proced. Int.* **2002**, *34*, 219.
7. Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; de los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401.
8. Gilchrist, T. L. *Aldrichim. Acta* **2001**, *34*, 51.
9. Hassner, A. *Adv. Strained Interesting Org. Mol.* **2000**, *8*, 187.
10. Smolinsky, G. *J. Am. Chem. Soc.* **1961**, *83*, 4483.
11. Alves, M. J.; Gilchrist, T. L. *Tetrahedron Lett.* **1998**, *39*, 7579.

12. Cyclobutadiene, another 4-π anti-aromatic system, is well known to be stabilized in π-coordinated complexes. Maitlis, P. M. *Adv. Organomet. Chem.* **1966**, *4*, 95.
13. Hassner, A.; Bunnell, C. A.; Haltiwanger, K. *J. Org. Chem.* **1978**, *43*, 57.
14. Hassner, A. *Azides and Nitrenes. Reactivity and Utility*; Academic Press: Orlando, 1984.
15. Padwa, A.; Blacklock, T.; Tremper, A. *Org. Synth. Coll.* **1988**, *Vol. 6*, 893.
16. Ray, J. K.; Gupta, S.; Pan, D.; Kar, G. K. *Tetrahedron* **2001**, *57*, 7213.
17. Konamata, N.; Nakata, T. *Heterocycles* **1998**, *48*, 2551.
18. Brahma, S.; Pan, D.; Ray, J. K. *Supramol. Chem.* **2005**, *48*, 447.
19. Data for the NMR experiment of compound **5a**: Initially the ^{1}H NMR spectrum of chloroaldehyde **5a** showed a signal for the aldehyde proton at 10.10 ppm and for C=C*H*–CHO at 6.94 ppm. Immediately after the addition of NaN_3, these two peaks were shifted upfield (10.10 ppm to 9.97 ppm and 6.94 ppm to 5.76 ppm), which clearly supported the formation of azido-aldehyde **6a**. Due to the formation of NaCl, we could not take further clear NMR spectra. So after work-up, followed by separation using preparative TLC, azirine **7a** (60%) and isoxazole **8a** (8%) were obtained.
20. Smolinsky, G. *J. Org. Chem.* **1962**, *27*, 3557.
21. Lwowski, W.; Mattingly, T. W., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1947.
22. We performed the complexation reaction of compounds **3a** and **7a** with $Pd(PhCN)_2Cl_2$. In the case of **3a**, after the addition of the Pd-salt into a solution in benzene-d_6, the doublet for the aldehyde proton at δ 8.70 ppm split into two sets of signals with a downfield shift of 0.16 ppm and in its mass spectrum (ES^+), the appearance of peaks at m/z 395.28, 396.01, 398.28, that is, for $[2M^+ + Pd]$ clearly showed that both azirine-ring nitrogens and the oxygens of both aldehydes were taking part in complexation. Whereas for **7a**, after similar treatment we obtained two types of signals for the aldehyde, one shifted downfield and other remained unchanged. In the mass spectrum (ES^+), peaks at m/z 441.84, 443.84, 445.84, that is, for $[M^+ + PdCl]$ clearly demonstrated that both nitrogen atoms from both azirine-rings and one carbonyl oxygen atom were involved in the coordination.