Pergamon

Tetrahedron Letters 40 (1999) 7163–7165

TETRAHEDRON
LETTERS

New synthesis of 2,2′-heteroarylpyrroles from heteroarylchlorocarbenes

Yuri N. Romashin,[a] Michael T. H. Liu,[a,*] Wei Ma[b] and Robert A. Moss[b,*]

[a] *Department of Chemistry, University of Prince Edward Island, Charlottetown, P.E.I., C1A 4P3 Canada*
[b] *Department of Chemistry, Rutgers University, New Brunswick, New Jersey 08903, USA*

Received 10 June 1999; accepted 14 July 1999

Abstract

2,2′-Pyridyl- and 2,2′-thienylpyrroles containing substituents at the 1- and 3-positions of the pyrrole ring have been prepared from the reaction of heteroarylchlorocarbenes with 1-azabuta-1,3-dienes. Laser flash photolysis of heteroarylchlorocarbene in isooctane in the presence of 1-azabuta-1,3-diene yields an azomethine ylide (λ=550 nm) as an intermediate. The kinetic parameters for the ylide formation and further 1,5-intramolecular cyclization to the pyrrole ring have been determined. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: diazirine; carbene; thienylpyrrole; pyridylpyrrole; azomethine ylide; azabutadiene; kinetics; laser flash photolysis.

Pyrroles represent an important class of heterocycles which have found many applications in medicine and technology. They have been extensively discussed in numerous monographs and reviews.[1] 2-Aryl- and 2-heteroarylsubstituted pyrroles are of great interest for the pharmaceutical industry,[1] for instance, as precursors in the synthesis of chemotherapeutics.[2] Some of them, especially thienylpyrroles, have served as prospective monomers for nonlinear optics materials[1,3,4] and organic conductive polymers.[4–6] The latter combine high electroconductivity, as well as thermal and environmental stability.[6] The synthesis of thienylpyrroles containing substituents at the 3-position of the heterocycles and/or at the nitrogen atom, attracts considerable attention because it makes it possible to modify the properties of polymers,[3,4] including the synthesis of chiral conducting polymeric materials.[4–7] Earlier[8] we reported a facile synthesis of 1,2,3-trisubstituted pyrroles by the reaction of arylchlorocarbenes with 1-azabuta-1,3-dienes under photolytic or thermal conditions. We applied this approach to the synthesis of 2,2′-heteroarylpyrroles.

Here we report the preparation of 2,2′-pyridylpyrroles and 2,2′-thienylpyrroles, containing substituents at the 1- and 3-positions of the pyrrole ring, from the reactions of 2-pyridyl- and 2-thienylchlorocarbenes with 1-azabuta-1,3-dienes under photolysis. We also conducted kinetics studies of the reactions of the carbenes with azabutadienes using laser flash photolytic (LFP) techniques in order to prove that the reactions involve azomethine ylides as intermediates, as we proposed earlier.[8] It is worth

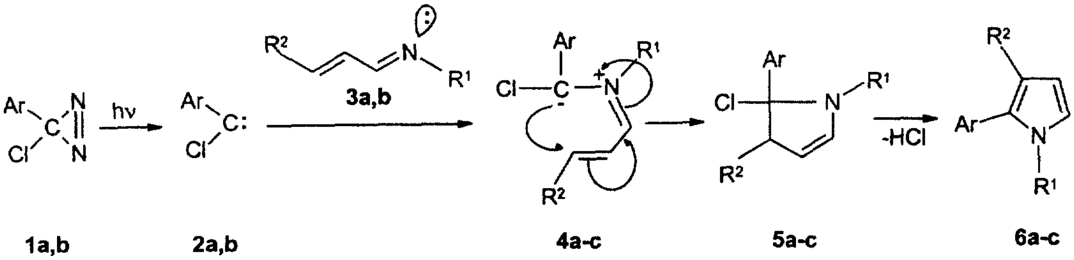
---

[*] Corresponding authors. Tel: +902 566 0565; fax: +902 566 0632; e-mail: liu@upei.ca

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01398-2

mentioning that the kinetics of thiophen-2-ylchlorocarbene under photolytic conditions have not been studied to date.

We prepared the heteroarylchlorodiazirines **1** by Graham oxidation of amidines,[9] and we generated the heteroarylchlorocarbenes **2** from heteroarylchlorodiazirines **1**[10,11] by photolysis (Scheme 1). We prepared 1-azabuta-1,3-dienes **3a,b** (R^1=Me, Bz; R^2=Me, Ph) from the reactions of cinnamaldehyde or crotonic aldehyde and methyl or benzyl amines. The yields and ^{1}H NMR data of the obtained products are presented in Table 1. NMR data compare well to those described in the literature[1,12] for thienylpyrroles.



1, 2 a Ar = 2-pyridyl; **b** Ar = 2-thienyl; **3 a** R^1 = Me, R^2 = Ph; **b** R^1 = Bz, R^2 = Me;

4-6 a Ar = 2-pyridyl, R^1 = Me, R^2 = Ph; **b** Ar = 2-thienyl, R^1 = Me, R^2 = Ph;

c Ar = 2-thienyl, R^1 = Bz, R^2 = Me

Scheme 1.

We carried out photolyses by irradiation (350 nm) of solutions of chlorodiazirines **1** (1 mmol) and 1-azabuta-1,3-dienes **3** (2.5 mmol) in hexane (50 ml) at 25°C for 24 h. After the workup, we purified the products **6a–c** by column chromatography on alumina with hexane:Et_2O (9:1) as eluent.

LFP irradiation[13] at 351 nm of a solution of 2-pyridylchlorodiazirine **1a** in isooctane at 25°C produces a transient absorption at 310 nm due to the formation of the 2-pyridylchlorocarbene **2a**, whose decay rate constant is $1.72\pm0.05\times10^6$ s^{-1}. In the presence of 1-azabuta-1,3-diene **3a**, a new transient, attributed to the azomethine ylide **4a**, grows in at 550 nm at a rate equal to that of the decay of the carbene measured at 310 nm. The plot of the observed pseudo-first-order rate constants against the concentration of azabutadiene **3a** is linear; the rate constant for the reaction of 2-pyridylchlorocarbene with 1-azabuta-1,3-diene **3a** is $k_{yl(4a)}=4.27\pm0.02\times10^9$ $M^{-1}s^{-1}$, and the intercept of the straight line ($1.98\pm0.1\times10^6$ s^{-1}) is the carbene **2a** decay rate constant in absence of **3a**, which is similar to that detected at 310 nm ($1.72\pm0.05\times10^6$ s^{-1}). The ylide **4a** (at 550 nm) decays with a lifetime equal to 23.5 μsec at 25°C, independent of the concentration of **3a**. Therefore, the rate constant for the 1,5-dipolar cyclization of **4a** to **5a** is $4.25\pm0.02\times10^4$ s^{-1}. HCl elimination from **5a** to yield pyrrole **6a** is likely to be fast since

Table 1

Isolated yields and ^{1}H NMR spectra of 2,2′-heteroarylpyrroles **6a–c**

Product	Yield, %	^{1}H-NMR (δ, $CDCl_3$)
6a	14	3.75 (3H, s, Me), 6.31 (1H, d, *J* = 3, 4-$H_{pyrrole}$), 6.75 (1H, d, *J* = 3, 5-$H_{pyrrole}$), 7.1-7.3 (3H, m, 3-$H_{pyridine}$, 4-$H_{pyridine}$, 5-$H_{pyridine}$), 7.4-7.6 (5H, m, Ph), 8.69 (1H, d, *J* = 7, 6-$H_{pyridine}$)
6b	15	3.59 (3H, s, Me), 6.44 (1H, d, *J* = 3, 4-$H_{pyrrole}$), 6.81 (1H, d, *J* = 3, 5-$H_{pyrrole}$), 7.0-7.1 (1H, m, 3-$H_{thiophene}$), 7.1-7.3 (6H, m, Ph, 4-$H_{thiophene}$), 7.4-7.5 (1H, m, 5-$H_{thiophene}$)
6c	14	2.17 (3H, s, Me), 5.08 (2H, s, CH_2), 6.15 (1H, d, *J* = 3, 4-$H_{pyrrole}$), 6.71 (1H, d, *J* = 3, 5-$H_{pyrrole}$), 6.8-6.9 (1H, m, 3-$H_{thiophene}$), 6.9-7.4 (7H, m, Ph, 4-$H_{thiophene}$, 5-$H_{thiophene}$)

no trace of **5a** can be detected. The aromatization of the system provides a strong driving force for this elimination. The temperature dependence (0–50°C) of the ylide **4a** yielded the following Arrhenius parameters: E_a=10.67±0.07 kcal mol^{-1} and A=2.76±0.05×10^{12} s^{-1} for cyclization to **5a**.

LFP of the solution of 2-thienylchlorodiazirine **1b** in isooctane at 25°C, produces a transient absorption at 310 nm due to the formation of the 2-thienylchlorocarbene **2b**, whose decay rate constant is 4.25±0.08×10^4 s^{-1}. In the presence of 1-azabuta-1,3-diene **3a**, a new transient, attributed to the azomethine ylide **4b** (λ=550 nm), grows at a rate equal to that of the decay of the carbene measured at 310 nm. The plot of the observed pseudo-first-order rate constants for the growth of the absorption at 550 nm versus the concentration of **3a** is linear; the rate constant for the reaction of 2-thienylchlorocarbene **2b** and **3a** at 25°C is $k_{yl(\mathbf{4b})}$=1.79±0.03×10^8 $M^{-1}s^{-1}$, and the intercept of the straight line (4.03±0.07×10^4 s^{-1}) is the carbene **2b** decay rate constant in the absence of **3a**. The ylide **4b** (at 550 nm) decays with a lifetime equal to 153 μsec at 25.4°C, independent of the concentration of **3a**. Therefore, the rate constant for the 1,5-dipolar cyclization of **4b** to **5b** is 6.54±0.02×10^3 s^{-1}. The temperature dependence (0–60°C) of the ylide **4b** yielded the following Arrhenius parameters: E_a=8.95±0.06 kcal mol^{-1} and A=2.69±0.04×10^{10} s^{-1} for the cyclization to **5b**.

2,2′-Pyridyl- and 2,2′-thienylpyrroles containing substituents at the 1- and 3-positions of the pyrrole ring have been prepared from the reactions of heteroarylchlorocarbenes with 1-azabuta-1,3-dienes. The present experiments also demonstrated the existence of azomethine ylides as intermediates in these reactions. The kinetics of the 1,5-dipolar cyclizations to yield the 2,2′-heteroarylpyrroles are reminiscent of the cyclization of 2-vinylpyridinium ylide.[14]

Acknowledgements

M. T. H. Liu and Yu. N. Romashin wish to thank the NSERC of Canada for its generous financial support. We express our gratitude to Diagnostic Chemicals Limited for recording the NMR spectra. R. A. Moss and W. Ma thank The National Science Foundation for financial support.

References

1. Katritzky, A. R.; Li, J.; Gordeev, M. F. *Synthesis* **1994**, 93–96.
2. Engel, N.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 676.
3. Lucchesini, F. *Tetrahedron* **1992**, *48*, 9951–9966.
4. Roncali, J. *Chem. Rev.* **1992**, *92*, 711–732.
5. (a) Kozaki, M.; Parakka, J. P.; Cava, M. P. *J. Org. Chem.* **1996**, *61*, 3657–3661; (b) Waltman, R. J.; Bargon, J. *Can. J. Chem.* **1986**, *64*, 76–95; (c) Patil, A. O.; Heeger, A. J.; Wudl, F. *Chem. Rev.* **1988**, *88*, 183–200.
6. Naitoh, S.; Sanui, K.; Ogata, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1348–1350.
7. (a) Zelikin, A.; Shastri, V. R.; Langer, R. *J. Org. Chem.* **1999**, *64*, 3379–3380; (b) Kotkar, D.; Joshi, V.; Ghosh, P. K. *J. Chem. Soc., Chem. Commun.* **1988**, 917–918.
8. Romashin, Yu. N.; Liu, M. T. H.; Bonneau, R. *Chem. Commun.* **1999**, 447–448.
9. Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396–4397.
10. Moss, R. A.; Jang, E. G.; Kim, H.-R.; Ho, G.-J.; Baird, M. S. *Tetrahedron Lett.* **1992**, *33*, 1427–1430.
11. Baird, M. S.; Bruce, I. *J. Chem. Research (M)* **1990**, 946–965.
12. Korostova, S. E.; Nesterenko, R. N.; Mikhaleva, A. I.; Polovnikova, R. I.; Golovanova, N. I. *Khim. Geterotsicl. Soedin.* **1989**, 901–906.
13. Moss, R. A.; Shen, S.; Hadel, L. M.; Kmiecik-Lawrynowicz, G.; Wlostowska, J.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1987**, *109*, 4341–4349.
14. Liu, M. T. H.; Romashin, Yu, N.; Bonneau, R. *Int'l. J. Chem. Kin.* **1994**, *26*, 1179–1184.