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Tetrahedron Letters 47 (2006) 353–356
Tetrahedron Letters

Intra- and intermolecular trapping of cyclopentapyrazine carbenes derived from 1,2-dialkynylimidazoles

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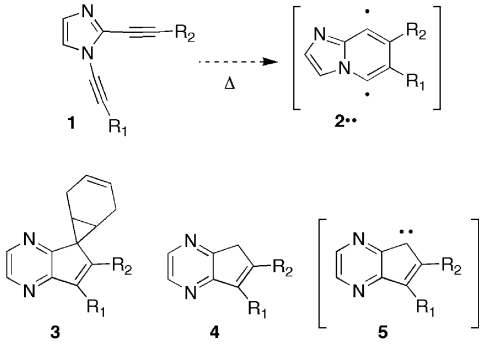
Received 19 October 2005; revised 1 November 2005; accepted 2 November 2005
Available online 18 November 2005

Abstract—The thermolysis of 1,2-dialkynylimidazoles in benzene solution affords high yields of 7-phenyl-5*H*-cyclopentapyrazines, which presumably form by solvent trapping of cyclopentapyrazine carbene intermediates. In cases where dialkynylimidazole contains side chains that can participate in intramolecular carbene C–H insertion or olefin addition, these processes compete with solvent addition to afford novel tri- and tetracyclic pyrazines, which can be obtained in good yield when the thermolysis is carried out in hexafluorobenzene.

1. Introduction

In our continuing studies of aza-variants of the diradical-generating Bergman[1] and Myers-Saito[2] cyclizations, we prepared the previously unknown 1,2-dialkynyl imidazoles (**1**).[3] Our expectation that mild thermolysis (75–100 °C) of **1** in 1,4-cyclohexadiene would lead to trapping of the 5,8-didehydroimidazo[1,2-*a*]pyridine diradicals **2**••, formed by aza-Bergman cyclization of **1** was not realized. Instead, we obtained mixtures of cyclopropanes **3** and the 5*H*-cyclopentapyrazines **4**, both presumably arising from the corresponding cyclopentapyrazine carbene **5** (Scheme 1).[4] While the mechanistic details of this rearrangement of **1** to **5** have not been fully addressed,[3] this cyclization is reminiscent of the carbene-generating cyclizations of enyne carbonyls,[5] enyne imines,[6] acyl ynimines,[7] and 2-ethynylphenyl di- and triazines.[8]

This rearrangement of **1** to **5** represents a novel approach to the synthesis of cyclopentapyrazines. While 5-alkyl-substituted cyclopentapyrazines are known as flavor agents isolated from roasted foodstuffs,[9] few examples of phenyl-substituted,[10] and polycyclic[11] cyclopentapyrazines have been prepared. Phenyl-substituted cyclopentapyrazines can be considered as analogs of phenyl pyrrolo[2,3-*b*]pyrazines, which are of interest as cyclin-dependent kinase inhibitors.[12,13] Polycyclic cyclopentapyrazines, such as analogs of the extremely cytotoxic cephalostatins,[14] are also of potential interest, both in terms of biological activity and as the building blocks for novel coordination compounds and materials.[15]



Scheme 1. Thermal rearrangement of 1,2-dialknylimidazoles to cyclopentapyrazine carbenes.

The synthetic utility of carbenes is well appreciated; and the thermal,[7,8] photochemical,[16] or metal-catalyzed[5,6,8] generation of carbenes or carbenoids from alkynes represents a growing area of interest. However, there are relatively few examples of cascade cyclizations involving carbenes formed by thermal cyclizations.[17] Here, we

Keywords: Cyclization; C–H Insertion; Cyclopropanation; Domino reactions; Thermal rearrangement.
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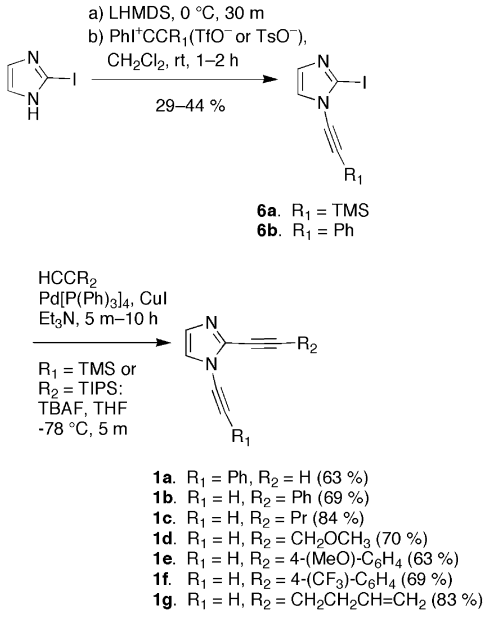
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.11.010

report the results of the thermolysis of **1** in benzene to give 7-phenyl-5*H*-cyclopentapyrazines in good yield. In cases where R_2 of **1** is propyl or butenyl, the intramolecular cyclization of the intermediate carbene **5** is a competitive side reaction with formal intermolecular C–H insertion reaction with benzene, affording moderate yields of polycyclic pyrazines. This intramolecular cyclization is the major reaction path when these thermolyses are carried out in hexafluorobenzene, leading to good yields of polycyclic pyrazines.

2. Results and discussion

1,2-Dialkynyl imidazoles were prepared from 2-iodoimidazole through N-alkynylation of the lithium anion with alkynyl iodonium triflates or tosylates[18] (Scheme 2). *N*-Alkynyl-2-iodoimidazoles **6a**,**b** undergo Sonogashira coupling[19] with a variety of terminal acetylenes to afford dialkynyl imidazoles in good yield. In the case of the coupling products of **6b**, treatment with TBAF afforded the desilylated dialkynylimidazoles **1b**–**g**.[20] Dialkynylimidazoles with terminal aryl substituents (**1a**,**b**,**e**,**f**) are isolated as stable solids; however, those with alkyl terminal substituents are somewhat unstable, turning dark upon storage under inert atmosphere in the freezer over the course of days to weeks.

Heating solutions of dialkynylimidazoles **1a**–**g** in benzene[21] leads to the formation of cyclopentapyrazines (Table 1).[22] Dialkynylimidazoles bearing terminal aryl substituents on either alkyne (**1a**,**b**,**e**,**f**) required more forcing conditions than those with alkyl (**1c**), alkenyl (**1g**), or alkoxyalkyl (**1d**) substituents, but in all cases, the reactions required a number of days to reach completion (Table 1). With the exception of dialkynylimidazoles **1c**,**d**,**g**, the exclusive products isolated after flash chromatography (SiO_2, 0–15% EtOAc/hexanes) of the reaction mixtures were the phenyl-substituted



Scheme 2. Synthesis of 1,2-dialkynylimidazoles.

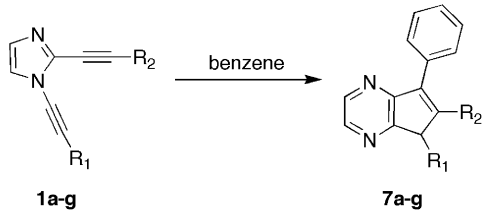
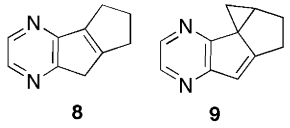


Table 1. Thermolysis of dialkynylimidazoles in benzene

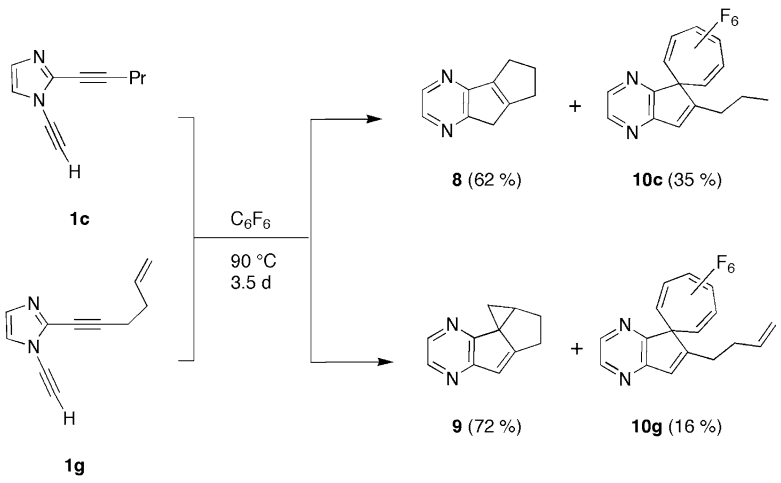
Series	Conditions	Yield of **7** (%)	Other products (yield)
a	100 °C, 2 d	88	
b	100 °C, 4 d	83	
c	80 °C, 5 d	72	**8** (17%)
d	80 °C, 2 d	38	
e	90 °C, 8 d	82	
f	90 °C, 8 d	82	
g	90 °C, 4 d	49	**9** (24%)



cyclopentapyrazines **7**, which are formed in good yields.[23] In the case of dialkynylimidazole **1d**, the isolated yield of **7d** was only moderate, and the formation of polymeric products, which were not further characterized, was noted. In the case of the propyl analogue **1c**, the intramolecular insertion product **8**[24] was isolated along with **7c** (1:4.2 ratio). The butenyl analog **1g** afforded the tetracyclic cyclopropane **9**[25] along with **7g** (1:2 ratio).

The structures of the phenyl-substituted cyclopentapyrazines **7a** and **7c** were established by high-resolution mass spectrometry (HRMS), and 2D NMR (COSY, NOESY, HMBC, and HMQC), which allowed unambiguous assignment of all the ^1H and ^{13}C NMR resonances. The other phenylcyclopentapyrazines were characterized by HRMS, ^1H, and ^{13}C NMR. The polycyclic cyclopentapyrazines **8** and **9** were characterized by HRMS, ^1H and ^{13}C NMR, and in the case of **9**, COSY NMR.

We did not detect or isolate any norcaradiene/cycloheptatriene products from these thermolyses in benzene, indicating that if these are formed as intermediates, they are rapidly converted to the phenyl-substituted products under these conditions. Alternatively, the formation of **7** may proceed through stepwise benzene C–H insertion[26] by the triplet carbene **5**, which is predicted to be lower in energy than the initially formed singlet.[4] Cyclopentapyrazines **7** and **8** were all isolated as the more stable, conjugated double-bond isomers, which is due to isomerization during the reaction. We note that when deuterated **1c** ($R_1 = D$) is subjected to thermolysis in benzene, deuterated **7c** ($R_1 = D$, 90% isotopic purity) is produced, as determined by ^1H NMR analysis of the crude reaction product. However, upon purification, there is substantial protium/deuterium exchange at the cyclopentapyrazine 5-position; the chromatographically isolated **7c** contains only 50% deuterium.



Scheme 3. Thermolysis of 1,2-dialkynylimidazoles in hexafluorobenzene favors intramolecular cyclization.

When solutions of dialkynyl imidazoles **1c** and **1g** in hexafluorobenzene were heated, the intramolecular trapping products were isolated in much higher yields than in benzene solvent (Scheme 3). However, even in the case of hexafluorobenzene, intermolecular addition to solvent occurs to give minor amounts of the fluorinated cycloheptatriene adducts **10c** and **10g**.[27] The assignment of the structures of these hexafluorinated cycloheptatrienes is based primarily on comparison of their ^{19}F NMR spectra to those reported for similar systems.[28] While clearly not inert to carbene **5**, hexafluorobenzene solvent has a diminished propensity to undergo addition with the carbene, which is not unexpected.[28,29] Importantly, this provides a convenient method to favor the intramolecular cyclization, leading to ratios of intra- to intermolecular products as high as 4.5:1 in the case of **1g**.

In summary, thermolysis of dialkynylimidazoles in benzene affords good yields of 7-phenyl-cyclopentapyrazines, and represents a novel entry into the cyclopentapyrazine ring system. Further evidence for a carbene intermediate **5** in the thermolysis of **1** has been obtained through identification of products derived from intramolecular C–H insertion and cyclopropanation. The formation of these polycyclic pyrazines **8** and **9** is the major pathway when these thermolyses are carried out in hexafluorobenzene. This provides a synthetically useful cascade cyclization process for the rapid assembly of structurally complex cyclopentapyrazines.

Acknowledgements

This work was supported by a Grant from the Robert Welch Foundation (F-1298).

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20. Representative spectral data (**1g**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, $J = 1.5$ Hz, 1H), 6.94 (d, $J = 1.5$ Hz, 1H), 5.87 (ddt, $J = 17.2$, 10.4, 6.4 Hz, 1H), 5.10 (dq $J = 16.8$, 1.6 Hz, 1H), 5.03 (dq, $J = 10.2$, 1.2 Hz, 1H), 3.12 (s, 1H), 2.54 (t, $J = 7.2$ Hz, 2H), 2.36 (q, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.09, 135.67, 129.05, 121.77, 116.09, 95.16, 71.00, 69.40, 61.38, 32.04, 19.09; HRMS (CI) *m/z* 171.0925 (Calcd 171.0922, $C_{11}H_{11}N_2$).
21. Caution: benzene is toxic and a carcinogen.
22. General procedure: dialkynylimidazoles **1a**–**g** (30 mg) in degassed benzene (4.5 mL) were heated in sealed reaction vials in an 80–100 °C oil bath with TLC monitoring until the starting material was consumed. The solvent was evaporated and the reaction products were purified by flash chromatography.
23. Representative spectral data (**7g**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (d, $J = 3$ Hz, 1H), 8.22 (d, $J = 3$ Hz, 1H), 7.50–7.46 (m, 4H), 7.41–7.37 (m, 1H), 5.82 (ddt, $J = 17.1$, 10.2, 6.6 Hz, 1H), 5.09–4.08 (m, 2H), 3.57 (s, 2H), 2.80 (t, $J = 7.8$ Hz, 2H), 2.41 (q, $J = 7.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.47, 158.05, 150.36, 141.87, 138.58, 138.51, 137.24, 132.63, 129.21, 128.49, 127.83, 115.68, 39.27, 33.26, 28.93; HRMS (CI) *m/z* 249.1390 (Calcd 249.1392, $C_{17}H_{17}N_2$).
24. Spectral data for **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, $J = 3.2$ Hz, 1H), 8.14 (d, $J = 3.2$ Hz, 1H), 3.36 (s, 2H), 2.82–2.74 (m, 4H), 2.43 (quintet, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.66, 158,89, 155.87, 146.72, 141.06, 137.32, 38.33, 35.33, 30.86, 27.10; HRMS 159.0928 (Calcd 159.0922, $C_{10}H_{11}N_2$).
25. Spectral data for **9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, $J = 3$ Hz, 1H), 8.03 (d, $J = 3$ Hz, 1H), 6.66 (br s, 1H), 2.64–2.60 (m, 2H), 2.49–2.44 (m, 2H), 2.36–2.32 (m, 1H), 2.24–2.10 (m, 1H), 1.68 (t, $J = 5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.95, 160.79, 159.64, 140.81, 136.66, 118.08, 44.77, 33.36, 29.27, 21.87, 19.44; HRMS 171.0924 (Calcd 171.0922, $C_{11}H_{11}N_2$).
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27. Data for **10c**: Melting point 58–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, $J = 3.2$ Hz, 1H), 8.17 (d, $J = 3.2$ Hz, 1H), 6.85 (br s, 1H), 2.48 (t, $J = 7.2$ Hz, 2H), 1.81 (sextet, $J = 7.2$ Hz, 2H), 1.08 (t, $J = 7.2$ Hz, 3H); partial ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.20, 156.35, 155.26, 145.16, 139.96, 129.81, 31.64, 20.44, 13.85; ^{19}F NMR (282 MHz, $CDCl_3$ referenced to $C_6F_6 = -163$ ppm): δ −123.07 (dt, $J = 8$, 4 Hz, 2F), −148.71 (m, 2F), −151.88 (m, 2F); HRMS 345.0814 (Calcd 345.0826, $C_{16}H_{10}F_6N_2$).
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