Arylchlorocarbenes in the synthesis of heterocycles containing two nitrogen atoms

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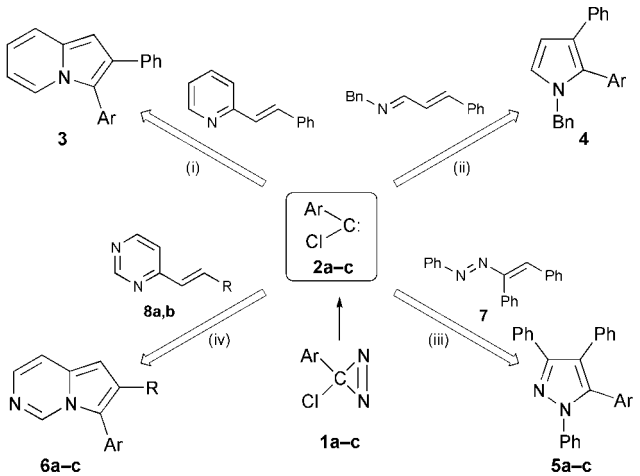
Substituted pyrazoles and pyrrolo[1,2-*c*]pyrimidines were prepared from the reaction of arylchlorocarbenes with 1,2-diazabuta-1,3-dienes and 4-vinylpyrimidines, respectively.

We recently reported the successful application of arylchlorocarbenes generated from arylchlorodiazirines to the synthesis of indolizines and pyrroles (Scheme 1, reactions (i) and (ii)).[1,2] The key step of the described approach produces a nitrogen ylide, followed by 1,5-intramolecular cyclization and HCl elimination. We now report further application of this methodology to the synthesis of a wider array of heterocycles containing two nitrogen atoms, such as pyrazoles and pyrrolo[1,2-*c*]pyrimidines (Scheme 1, reactions (iii) and (iv)). Pyrazoles have attracted the attention of many chemists because of their applications in organometallic chemistry as ligands, in synthesis, in particular of bioactive compounds, as well as their thermal reactions, spectroscopic applications and theoretical calculations.[3] Pyrrolo[1,2-*c*]pyrimidines, the aza analogues of indolizines, have attracted substantial interest because of their ability to facilitate easy ring cleavage, their variety of ring transformations and recyclizations,[4] and for their role as starting materials to N-bridged heteroaromatics.[5] However, the known synthetic routes to these compounds are lengthy and result in poor yields.[5,6] In this respect, these highly reactive carbenes have been harnessed and utilized to achieve difficult synthetic tasks which other reactive intermediates cannot easily perform.

The arylchlorocarbenes **2a–c** were generated from arylchlorodiazirines **1a–c**[7] by thermolysis. Phenylazostilbene **7** was prepared from acetoxydeoxybenzoin and phenylhydrazine.[8] Thermolysis of arylchlorodiazirines **1a–c** in the presence of phenylazostilbene **7** leads to 1,3,4,5-tetrasubstituted pyrazoles **5a-c** in good yield (74–83%). Attanasi and coworkers have developed an effective approach to pyrazoles based on a preliminary 1,4-addition of a nucleophilic reagent to the 1,2-diazabuta-1,3-diene substrates, which also gave a 70–80% product yield.[9] Vinylpyrimidines **8a,b** were prepared from 4-methylpyrimidine according to previously described procedures.[10,11] Thermolysis of arylchlorodiazirines **1a-c** in the presence of vinylpyrimidines **8a**,**b** leads to 6,7-disubstituted pyrrolo[1,2-*c*]pyrimidines **6a–c** in a 17–22% yield. The yields and physical data of obtained pyrazoles **5a–c** and pyrrolopyrimidines **6a–c** are given in ref. 12.†



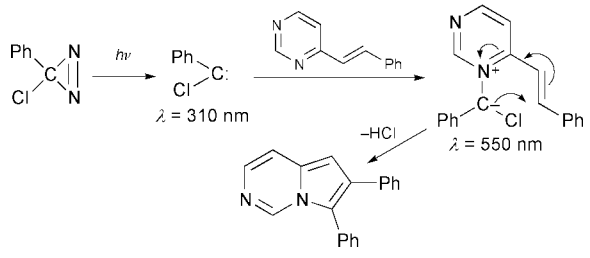
1,2,5: **a** Ar = Ph, **b** Ar = *p*-MeC_6H_4, **c** Ar = *p*-ClC_6H_4
6: **a** R = H, Ar = *p*-ClC_6H_4, **b** R = Ph, Ar = *p*-MeC_6H_4, **c** R = Ph, Ar = *p*-ClC_6H_4
8: **a** R = H, **b** R = Ph

Scheme 1

In general, solutions of chlorodiazirine **1a–c** (2 mmol) and phenylazostilbene **7** or vinylpyrimidine **8a**,**b** (1 mmol) were refluxed in absolute benzene (10 mL) for 24 h. After workup, the pyrazoles **5a–c** were purified by column chromatography on silica gel with 10 : 1 hexane–diethyl ether eluent, followed by crystallization from propan-2-ol–hexane (1 : 3); pyrrolopyrimidines **6a–c** were purified by column chromatography on Al_2O_3 (basic) with 4 : 1 hexane–diethyl ether eluent.

Vinylpyrimidines **8a**,**b** are transparent at 351 nm, which is not the case for phenylazostilbene **7**. In order to learn whether the reaction of chlorodiazirines **1a–c** with vinylpyrimidines **8a**,**b** goes through an N-ylide intermediate, we undertook laser flash photolysis (LFP) studies[14] of this system to examine the kinetics of nitrogen ylide formation and the rate of 1,5-dipolar cyclization.

LFP irradiation at 351 nm of a solution of chlorophenyldiazirine **1a** in benzene (A = 1.0 at λ = 376, 392 nm) at 25 °C produces a transient absorption at 310 nm due to the formation of the chlorophenylcarbene **2a**, whose decay rate constant is 2.02×10^5 s^{-1}. In the presence of pyrimidine derivative **8b**, a new transient attributed to the pyrimidinium ylide appears at 550 nm. The plot of the observed pseudo-first-order rate constants for the growth of the absorption at 550 nm *vs.* concentration of **8b** is linear, and the rate constant for the reaction of chlorophenylcarbene **2a** and pyrimidine **8b** at 25 °C is $k_{ylide} = 3.24 \times 10^8$ $M^{-1}s.^{-1}$ The intercept of the straight line (2.78×10^5 s^{-1}) is the chlorophenylcarbene **2a** decay rate constant in the absence of **8b**, which is similar to that detected at 310 nm (2.02×10^5 s^{-1}). The pyrimidinium ylide (at 550 nm) decays in benzene with a lifetime equal to 102.2 μs at 22 °C, independent of the concentration of **8b**. Therefore, the rate constant for the 1,5-dipolar cyclization of pyrimidinium ylide is $k_{1,5\text{-cycl}} = 9.78 \times 10^3$ s^{-1}. The temperature dependence (0–55 °C) of the pyrimidinium ylide decay to form the



Scheme 2

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1,5-cyclization product yielded the following Arrhenius parameters: E_a = 10.0 kcal mol^{-1} and A = 2.36 × 10^{11} s^{-1}.

We have shown that chlorocarbenes can be successfully applied to the synthesis of 1,3,4,5-tetrasubstituted pyrazoles and 6,7-disubstituted pyrrolo[1,2-*c*]pyrimidines. This methodology is simple and effective. We have also demonstrated the existence of nitrogen ylides as intermediates in these reactions. The kinetics of the 1,5-dipolar cyclizations of pyrimidinium ylides to yield pyrrolo[1,2-*c*]pyrimidines are reminiscent of the cyclization of 2-vinylpyridinium ylides to indolizines[1] and azomethine ylides to pyrroles.[2]

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Notes and references

† All compounds reported herein gave satisfactory microanalysis data.

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12 Data for 1,3,4,5-tetraphenylpyrazole **5a**: 78% yield; mp 217.5–218.5 °C [lit.[13]: mp 217–218 °C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.0–7.4 (18H, m), 7.5–7.6 (2H, m). For 1,3,4-triphenyl-5-(*p*-methylphenyl)pyrazole **5b**: 83% yield; mp 173–174 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (3H, s), 6.9–7.4 (17H, m), 7.5–7.6 (2H, m); MS: *m*/*z* 386 (100), 385 (51%). For 1,3,4-triphenyl-5-(*p*-chlorophenyl)pyrazole **5c**: 74% yield; mp 178–179 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.9–7.4 (17H, m), 7.5–7.6 (2H, m); MS: *m*/*z* 408 (33), 406 (100%). For 7-(*p*-chlorophenyl)pyrrolo[1,2-*c*]pyrimidine **6a**: 17% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.53 (1H, d, J = 3.5, 5-H_{pyr}), 6.90 (1H, J = 3.5 Hz, 6-H_{pyr}), 7.2–7.3 (2H, m, C_6H_4), 7.4–7.6 (4H, m, 3-H_{pyr}, 4-H_{pyr}, C_6H_4), 9.04 (1H, s, 1-H_{pyr}); MS: *m*/*z* 230 (34), 228 (100), 193 (16), 192 (18%). For 6-phenyl-7-(*p*-methylphenyl)pyrrolo[1,2-*c*]pyrimidine **6b**: 17% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (3H, s, Me), 6.65 (1H, s, 5-H_{pyr}), 7.1–7.5 (11H, m, 3-H_{pyr}, 4-H_{pyr}, Ph, C_6H_4), 8.76 (1H, s, 1-H_{pyr}). For 6-phenyl-7-(*p*-chlorophenyl)pyrrolo[1,2-*c*]pyrimidine **6c**: 22% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (1H, s, 5-H_{pyr}), 7.2–7.5 (11H, m, 3-H_{pyr}, 4-H_{pyr}, Ph, C_6H_4), 8.79 (1H, s, 1-H_{pyr}); MS: *m*/*z* 306 (33), 304 (100).

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14 These experiments were performed with a Lambda Physik COMPex model 120 excimer laser using a Spectra Gases filled with 0.1875% F_2, 0.468% Xe, and 99.334% Ne. The sample in a 10 × 10 mm cell was excited at 351 nm by single light pulses (10 ns; 40 mJ). The detection unit comprised a 1000 W Oriel xenon arc lamp, a 1 in. Uniblitz shutter, Instruments SA grating monochromator, and a RCA 4840 photomultiplier tube wired in a 5-dynode configuration. The data collection and analysis system included a Stanford Research Systems model DG535 4-channel digital delay/pulse generator and a Tektronix TDS 320 2-channel oscilloscope.