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2-Thienylchlorocarbene: reactivity toward alkenes

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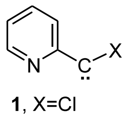
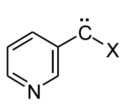
Abstract—Absolute rate constants for the additions of *syn*- and *anti*-2-thienylchlorocarbenes to various alkenes have been measured. The reactivity, selectivity, and structures of these species were characterized experimentally and computationally.

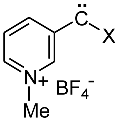
The addition of heteroarylcarbenes to alkenes affords heteroarylcyclopropanes, an entry to novel heterocyclic compounds. Thus, 2-pyridylchlorocarbene (**1**),[1] 3-pyridylchlorocarbene (**2**),[1] the corresponding fluorocarbenes[2] **3** and **4**, as well as the *N*-methyl-3-pyridiniumhalocarbenes[2] **5** and **6**, add readily to alkenes. Similarly, 2-thienylchlorocarbene (**7**, 2-ThCCl) and 3-thienylchlorocarbene cyclopropanate a variety of olefins.[3,4] Additionally, carbenes **1** and **7** can be trapped by 1-azabuta-1,3-dienes to furnish 2,2′-pyridyl- and 2,2′-thienylpyrroles via azomethine ylides.[5] The furyl analogue of **7**, 2-furylchlorocarbene, also adds to alkenes, although its facile ring-opening reaction renders its chemistry more complex than that of **7**.[6]



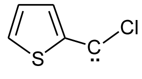
1, X=Cl
3, X=F



2, X=Cl
4, X=F



5, X=Cl
6, X=F

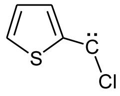


7 (2-ThCCl)

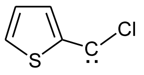
Absolute rate constants for the additions of carbenes **1** and **2** to a spectrum of electron-rich and electron-poor alkenes were determined by laser flash photolysis (LFP),[2] and are consistent with an *ambiphilic* selectivity pattern[7] for both carbenes: rapid reaction with both electron-rich and electron-poor alkenes, but slower addition to electronically non-descript olefins (e.g. 1-hexene). The alkene selectivities of carbenes **1** and **2** resemble that of phenylchlorocarbene (PhCCl), although they are several times more reactive than PhCCl toward a given substrate.[2,7b]

The selectivity of 2-ThCCl has been studied[4] by relative reactivity (competition) experiments,[8] using the 'standard set' of alkene substrates.[7d,9] Toward these (electron-rich) olefins, 2-ThCCl behaved as an electrophile, affording a carbene selectivity index,[7] $m_{\mathrm{CXY}} = 0.95$[4] (relative to $m_{\mathrm{CCl_2}} = 1.00$) somewhat more selective than PhCCl ($m_{\mathrm{PhCCl}} = 0.83$[7d]).

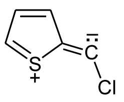
Here, we present LFP and computational studies of 2-ThCCl which enhance our understanding of its reactivity. In particular, we find that it is an ambiphilic carbene, that it is somewhat less reactive but more selective than PhCCl, that both *syn* and *anti* isomers of ThCCl (*syn*-**7** and *anti*-**7**) can be observed in solution by LFP, and that both carbene isomers react with alkenes at rather similar rates.



syn-**7**



anti-**7**



syn-**7'**

2-Thiophenecarboxamidine hydrochloride[10] in DMSO saturated with LiCl was oxidized to 3-chloro-3-(thiophen-2-yl)diazirine (**8**) by aqueous NaOCl saturated with NaCl (Graham oxidation).[4,11,12] Approximately 5 mmol of freshly prepared diazirine **8** was irradiated (focused 200 W Oriel UV lamp, $\lambda > 320$ nm, 2 h) in 2 ml of alkenes **9a**–**f**, forming cyclopropanes **10a**–**f** in 55–74% yields (based on 2-thiophenecarboxyamidine) (Scheme 1).

Cyclopropanes **10c**–**f** were purified by chromatography on silica[13] and characterized by appropriate ^{1}H and ^{13}C NMR spectra and GC MS (M^+). Cyclopropanes **10a**, **10b**, and **10e** were previously described by Baird and

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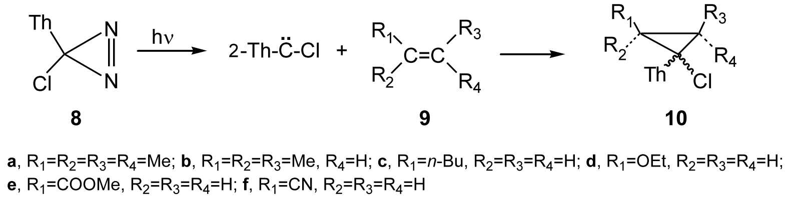
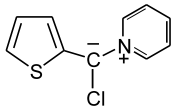


Scheme 1.

Bruce.[4] Cyclopropanes **10b–f** were each mixtures of *syn* and *anti* diastereomers.[4]

Absolute rate constants for the additions of 2-ThCCl to alkenes **9a–f** were determined by LFP.[14] LFP (351 nm, 80 mJ) of diazirine **8** ($A_{388}=0.5$) in pentane afforded 2-ThCCl; the 20 ns 'point-by-point' LFP-UV spectrum appears in Figure 1. The distinct maxima at ca. 328 and 310 nm are assigned to *syn*-**7** and *anti*-**7**, respectively, based on transition dipole calculations which predict these transitions at 317 and 294 nm in vacuo. Although the match is not exact, the observed (18 nm) and computed (23 nm) separations are similar. We compute barriers of 19.6 kcal/mol for *syn*-**7**→*anti*-**7** and 17.3 kcal/mol for the reverse process; interconversion of these species will not occur on the μs timescale of the ThCCl-alkene addition reactions.[15] Analogous 'isomers' of 2-furylchlorocarbene have been observed by IR in nitrogen matrices at 8 K.[6]

Both carbene signals are quenched by pyridine with the appearance of a new transient at 550 nm, attributed to pyridinium ylide **11**. From a linear correlation ($r=0.986$, 9 points) of the apparent pseudo-first-order rate constant (~2×10^6–1.6×10^7 s^{-1}) for the formation of **11** vs the concentration of pyridine in pentane (0.02–0.2 M), we find $k_y=4.1\times10^7$ M^{-1} s^{-1} for the formation of the ylide at 25°C. This is significantly lower than the analogous value for PhCCl (1.5×10^9 $M^{-1}s^{-1}$ at −32°C),[16] suggesting that 2-ThCCl is less reactive than PhCCl. Trapping experiments with alkenes support this view.



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LFP generation of 2-ThCCl in pentane solutions of alkenes **9a–f** led to quenching of the carbene isomers' absorptions at 328 and 310 nm. Correlations at 328 nm of the apparent pseudo-first-order rate constants for quenching of *syn*-**7** with alkene concentration were linear ($r>0.994$, except for **9d**, where $r=0.986$); the slopes afforded second order rate constants (k_2) for the carbene–alkene addition reactions of Scheme 1; cf., Table 1, which includes analogous rate constants for PhCCl.[17]

Quenching experiments were also monitored at 310 nm (*anti*-**7**) with tetramethylethylene, 1-hexene, methyl acrylate, and acrylonitrile. The observed rate constants (M^{-1} s^{-1}) were $5.3\pm0.3\times10^7$, $2.0\pm0.06\times10^5$, $6.5\pm0.5\times10^5$,

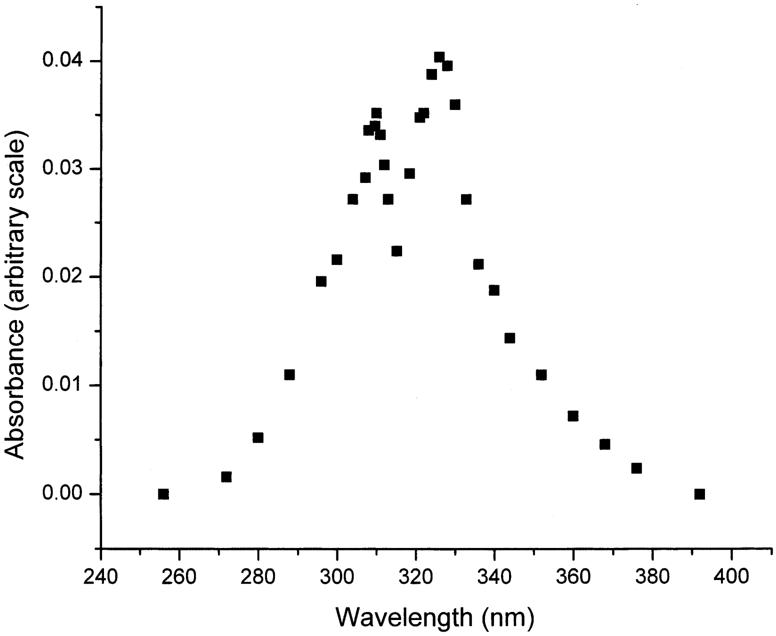

Figure 1. LFP UV spectrum of *syn*-2-thienylchlorocarbene (*syn*-**7**, λ_{max} 328 nm) and *anti*-2-thienylchlorocarbene (*anti*-**7**, λ_{max} 310 nm).

Table 1. Rate constants for carbene–alkene additions of 2-ThCCl

Alkene	k_2(2-ThCCl) (M^{-1} s^{-1})[a]	k_{rel}[b]	k_{rel}(exp)[c]	k_2(PhCCl) (M^{-1} s^{-1})[d]
$Me_2C{=}CMe_2$	$3.8\pm0.3\times10^7$	1.0	1.0	2.8×10^8
$Me_2C{=}CHMe$	$6.2\pm0.1\times10^6$	0.16	0.21	1.3×10^8
$CH_2{=}CHC_4H_9$	$1.8\pm0.2\times10^5$	0.0047	0.0019	2.2×10^6
$CH_2{=}CHOEt$	$1.3\pm0.16\times10^5$	0.0034	0.0045	5.01×10^{5e}
$CH_2{=}CHCOOMe$	$5.6\pm0.05\times10^5$	0.015	0.024	5.1×10^6
$CH_2{=}CHCN$	$1.3\pm0.01\times10^6$	0.034	0.065	5.4×10^6

[a] Absolute rate constants for additions of 2-ThCCl measured by LFP at 25°C; the decay of *syn*-**7** was followed at 328 nm; see text.

[b] Relative rate constants derived from k_2 assigning $k_{rel}(Me_2C{=}CMe_2)=1.0$.

[c] Relative rate constants determined experimentally; see text.

[d] Absolute rate constants for additions of PhCCl; see Refs. 7b and 17.

[e] This work.

and 5.1±0.5×10^5, respectively. Comparison with the analogous values for *syn*-**7** in Table 1 shows that *syn*-**7** adds about twice as fast as *anti*-**7** to acrylonitrile, but both isomers of 2-ThCCl react with alkenes at rather similar rates.

We also determined relative reactivities for the additions of 2-ThCCl to the various alkenes. Here, pairs of (excess) alkenes compete for an insufficiency of carbene, and k_{rel} is assessed from the initial alkene mole ratio and the mole ratio of the corresponding product cyclopropanes.[4,8] The product-based relative reactivities, normalized to $Me_2C{=}CMe_2$, appear in Table 1, and are in reasonable agreement with k_{rel} values derived from the measured absolute rate constants.[18]

From Table 1, it is clear that 2-ThCCl, like PhCCl,[7,17b,c] is ambiphilic[7] toward the selected set of alkenes: both carbenes select electrophilically toward electron-rich alkenes ($Me_2C{=}CMe_2$, $Me_2C{=}CHMe$), but nucleophilically toward electron-poor alkenes ($CH_2{=}CHCOOMe$, $CH_2{=}CHCN$). They are less reactive toward 1-hexene or ethyl vinyl ether. The pyridylchlorocarbenes, **1** and **2**, exhibit similar ambiphilic selectivity.[2]

The earlier relative reactivity studies of 2-ThCCl by Baird and Bruce[4] employed electron-rich alkenes which revealed only the electrophilic segment of the carbene's overall ambiphilic reactivity. The carbene selectivity index (m_{CXY}) of 2-ThCCl, derived from product-based relative reactivities, is 0.95.[4] The comparable value for PhCCl is 0.83,[7d] so that 2-ThCCl is somewhat more selective than PhCCl. Moreover, the absolute rate constants of Table 1 show that 2-ThCCl is also less reactive than PhCCl toward a given alkene: k_2(PhCCl)/k_2(2-ThCCl) ranges from 3.8 for ethyl vinyl ether to ~21 for trimethylethylene. The greater selectivity of 2-ThCCl between alkenes, coupled with its lower reactivity toward specific alkenes, constitutes 'normal' reactivity-selectivity behavior.

Qualitatively, the lower reactivity of 2-ThCCl vs PhCCl can be attributed to greater electron release by the 2-thienyl group (vs phenyl), as represented by resonance contributor **7′**. Electron donation to the carbenic carbon of 2-ThCCl stabilizes this carbene, and enhances its selectivity relative to PhCCl, where this effect is less important.[19] In contrast, 2- and 3-pyridylchlorocarbenes **1** and **2** are more reactive than PhCCl toward the alkenes of Table 1, presumably due to greater inductive electron-withdrawal by the pyridyl versus the phenyl group, which destabilizes carbenes **1** and **2** and boosts their reactivity.[1]

Complete geometry optimizations of *syn*-**7** and *anti*-**7** were carried out at the HF/6-31G* and B3LYP/6-31G* levels using the Gaussian98 suite of programs.[20] All stationary points were characterized by normal coordinate analyses, and energies were corrected for thermal effects and zero point energies.

We find *syn*-**7** to be more stable than *anti*-**7** by 2.30 kcal/mol with interconversion barriers of 19.6 (*syn*→*anti*) or 17.3 (*anti*→*syn*) kcal/mol (DFT), respectively. For the furylchlorocarbene analogues of **7**, the *syn* carbene has also been computed (by DFT) to be more stable than its *anti* relative ($\Delta E = 1.3$ kcal/mol).[6]

2-ThCCl is computed to be a ground state singlet carbene, which accords with its observed[4] stereospecific additions to *cis*-and *trans*-butene. The computed $\Delta E_{S\text{-}T}$ values are −9.6 (*syn*-**7**) and −8.0 (*anti*-**7**) kcal/mol, but they should be considered tentative because of significant occupancy of some of the virtual orbitals in both singlet and triplet states at the B3LYP/6-31G* level. For comparison, the computed $\Delta E_{S\text{-}T}$ ranges from −4 to −8 kcal/mol for PhCCl, with a 'best' value of −7.84 kcal/mol.[21]

The computed C–C–Cl bond angles of *syn*-**7** and *anti*-**7** are 111.7° and 110.2°, respectively, consistent with singlet state species; the comparable value for singlet PhCCl is computed at 112–113° (we calculate 111.9°), whereas it is ~131° for triplet PhCCl.[21] Importantly, we compute the 2-ThCCl C(2)–C(carbene) bond lengths at 1.411 Å (*syn*-**7**) and 1.418 Å (*anti*-**7**). These 'short' C–C bonds are consistent with the resonance donation depicted in structure **7′**. The comparable C–C bond in PhCCl is computed at 1.457 Å, supporting the notion that resonance electron donation from the aromatic residue to the carbenic center is stronger in 2-ThCCl than in PhCCl, and so contributes to the former's lower reactivity and higher selectivity.

Finally, HOMO and LUMO energies were computed for 2-ThCCl and PhCCl at the HF/6-31G* level (for consistency with earlier work[7,22]). The comparable orbital energies (eV) were quite similar: HOMOs, *syn*-**7** (−9.57), *anti*-**7** (−9.67), PhCCl (−9.55); LUMOs, 0.79, 0.71, and 0.97, respectively. Calculations of the differential orbital energies,[7,22] (LUMO-π) and (π*-HOMO) for additions of *syn*-**7** to the alkenes of Table 1 indicate that the (LUMO-π) 'electrophilic' interaction will dominate the additions of 2-ThCCl to Me_2C=CMe_2, Me_2C=CHMe, and CH_2=CHC_4H_9, but that the (π*-HOMO) 'nucleophilic' interaction will control the carbene's addition to CH_2=CHCOOMe and CH_2=CHCN.[23] The calculations are thus in accord with the observed ambiphilicity of 2-ThCCl.

Acknowledgements

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12. The orange, oily diazirine was obtained in 86% yield after chromatography on silica gel with pentane elution. It is unstable at ambient temperature, but can be stored for several days at −10°C, or longer when diluted with pentane. ^{1}H NMR (δ, $CDCl_3$): 7.27 (d, J=4.5 Hz, 1H), 6.98 (dd, J=4.5, 3.6 Hz, 1H), 6.75 (d, J=3.6 Hz, 1H).
13. Cyclopropane **10a** very readily ring-opens upon chromatography with loss of HCl to yield 2,4-dimethyl-3-(thiophen-2-yl)-1,3-pentadiene.[4]
14. For a description of our LFP system, see Moss, R. A.; Johnson, L. A.; Merrer, D. C.; Lee, G. E., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 5940. The system has been upgraded by the incorporation of a 150 W pulsed Xe monitoring lamp.
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18. Note that k_{rel} values based on the absolute rate constants in Table 1 reflect the reactivity only of *syn*-**7**, whereas the product-based k_{rel}(exp) values reflect the reactivity of *both syn-* and *anti*-**7**.
19. The σ^+ constant of 2-thienyl ranges from ∼−0.68 to −0.87 on a scale where σ^+(Ph)=0. See Hill, E. A.; Gross, M. L.; Stasiewicz, M.; Manion, M. *J. Am. Chem. Soc.* **1969**, *91*, 7381. Smith, G. G.; Kirby, J. A. *J. Heterocyclic Chem.* **1971**, *8*, 1101. More precisely, σ_R^+ for 2-thienyl is −0.37 (private communication from Professor M. Charton, 23 September, 2002) on a scale where σ_R^+ for phenyl is −0.30. Thus, 2-ThCCl should be, as observed, somewhat more selective than PhCCl, although the strength of the resonance donation depicted in structure **7′** is not nearly great enough to make 2-ThCCl a 'nucleophilic' carbene. Its computed[7d] carbene selectivity index ($m_{2\text{-}ThCCl}$) is 0.83 (experimental value 0.95[4]), well to the electrophilic side of even the classic ambiphile, MeOCCl (calculated m_{CXY}=1.59).[7d]
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23. The differential orbital energies (eV) are [alkene, (LUMO-π), (π*-HOMO)]: Me_2C=CMe_2, 9.06, 11.85; Me_2C=CHMe, 9.47, 11.81; CH_2=CHC_4H_9, 10.31; 11.56; CH_2=CHOEt, 9.86, 11.63; CH_2=CHCOOMe, 11.51, 10.37; CH_2=CHCN, 11.71, 9.78. The smaller differential orbital energy in each case correlates with the dominant orbital interaction in the addition transition state.[7]