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Reaction of a stable aminoarylcarbene with 2-chloroacrylonitrile: dearomatizing cyclization rather than cyclopropanation

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Abstract—The reaction of a stable aminoarylcarbene with 2-chloroacrylonitrile is reported. The resulting 1/1 adduct has been spectroscopically and structurally characterized. The initial Michael addition is not followed by cyclopropane formation but by a dearomatizing cyclization affording an original bicyclic structure.

Cyclopropanes are attracting considerable interest both as synthetic intermediates and as biologically relevant moieties of constrained geometry. Their preparation is most widely achieved by the so-called cyclopropanation reaction, that is the formal addition of a carbene to an alkene. Both singlet and triplet transient carbenes undergo cyclopropanation reactions, although with a totally different mechanism.[1] Cyclopropanes can also be obtained from metal–carbene complexes,[2] and accordingly, metal-assisted syntheses have been developed both in stoichiometric and catalytic versions.[3]

Over the last 15 years, the availability of stable singlet carbenes[4] has allowed for a better understanding of the factors governing the stereoselectivity of this reaction. Indeed, diastereo- as well as enantioselective cyclopropanation reactions were observed for stable phosphinocarbenes.[5] In marked contrast, no cyclopropanation reaction has been reported for stable aminocarbenes,[6–9] most probably because of the stronger donation of the amino compared to phosphino substituent, which makes the carbene vacant orbital higher in energy. For example, nucleophilic attack of the 1,3,4-triphenyl-1,2,4-triazol-5-ylidene on dimethylfumarate or dimethylmaleate is not followed by ring closure leading to the corresponding cyclopropanes (Scheme 1), but rather by a 1,2-proton shift, affording a methylenetriazoline.[9b,c]

We have recently described the synthesis of persistent and even stable aminoarylcarbenes.[10] This prompted us to investigate their behavior toward alkenes, and here we report a new competitive pathway for cyclopropanation, namely an original dearomatizing cyclization.

Following Moss' classification,[11] and despite the presence of the inductively withdrawing 2,6-bis(trifluoromethyl)phenyl substituent (Ar_F), the aminoarylcarbene **1**[10a] can be expected to feature nucleophilic character toward alkenes. Accordingly, no reaction was observed with electron-rich olefins such as enol ethers or enamines. We then investigated the reaction of **1** with 2-chloroacrylonitrile, since this highly electron-deficient olefin[12] had been previously demonstrated to react with the related phosphinoarylcarbene $(i\text{-Pr}_2\text{N})_2\text{PCAr}_F$ affording a 3:1 mixture of the corresponding cyclopropanes.[13] According to ^{19}F NMR, the conversion of **1** was complete after 2 h at room temperature in tetrahydrofuran. After removal of the solvent under vacuum, the resulting product **2** was extracted with pentane and characterized spectroscopically.[14] The expected

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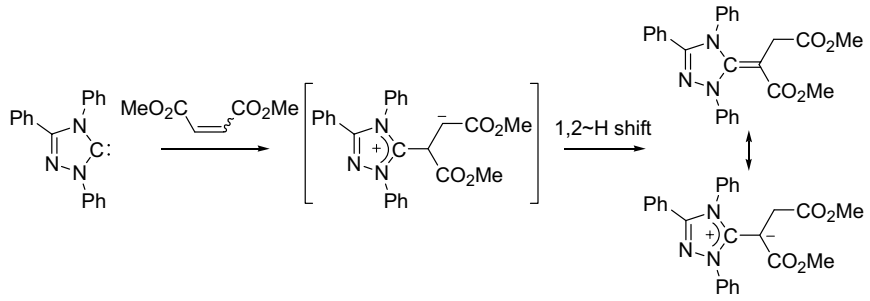


Scheme 1. Abnormal cyclopropanation reactions of the 1,3,4-triphenyl-1,2,4-triazol-5-ylidene with dimethyl-fumarate and maleate.

formation of a 1/1 adduct between the carbene and olefin was established by mass spectrometry (DCI/NH_3). The ^1H NMR spectrum indicated the presence of two diastereotopic protons for a methylene group (δ 3.19 and 3.55 ppm, $^2J_{HH} = 17.3$ Hz), but the corresponding ^{13}C signal (δ 50.4 ppm) was about 20 ppm at lower field than that expected for a cyclopropane.[13] Moreover, the ^{19}F NMR spectrum featured a signal in the typical range for a $C(sp^2)CF_3$ group (δ 14.4 ppm) but also another one of similar intensity at much higher field (δ 1.9 ppm). This suggested the desymmetrization of the 2,6-bis(trifluoromethyl)phenyl framework, which was further corroborated by the magnetic inequivalence of the CH_{meta} groups of **2** (^1H: δ 6.11 and 6.48 ppm, d, $^3J_{HH} = 5.7$ Hz and ^{13}C: δ 126.6 and 127.0 ppm). These data as a whole were not in favor of a cyclopropane moiety. Single crystals of **2** were grown from a saturated pentane solution at −30 °C and the X-ray diffraction study revealed an original bicyclic structure, the two carbon atoms of the olefin bridging the carbene center and one of the *ortho* positions of the Ar_F ring (Fig. 1).

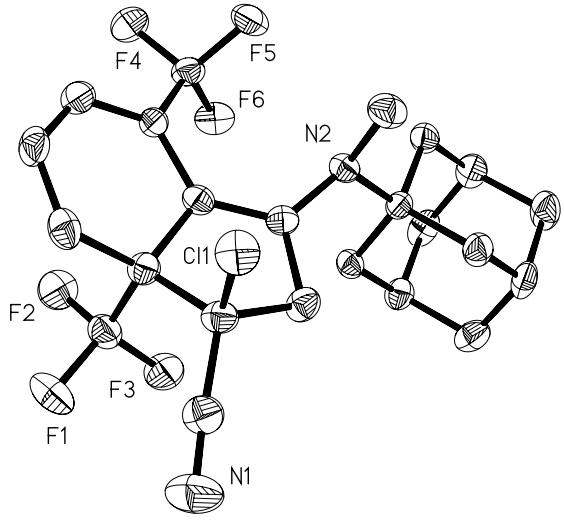
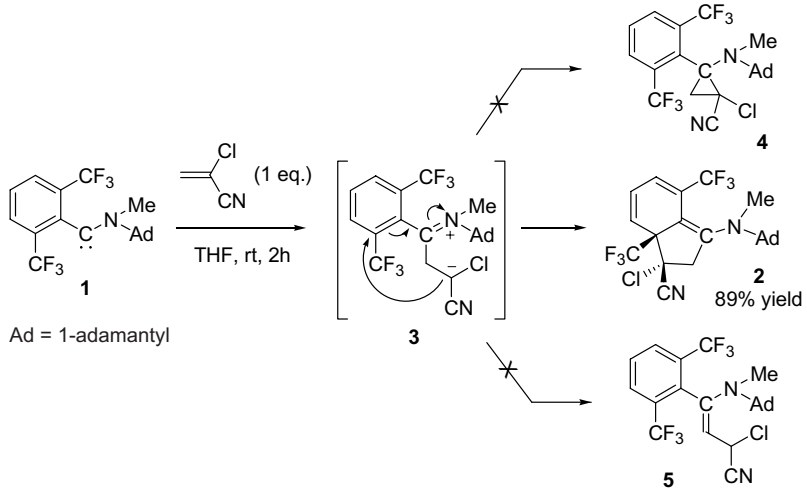


Figure 1. Thermal ellipsoid diagram (50% probability) of **2**, the hydrogen have been omitted for clarity.

From a mechanistic point of view, the formation of **2** most probably results from a Michael addition of the carbene to the olefin, followed by dearomatizing cyclization of the resulting zwitter-ion **3** via nucleophilic attack at one of the *ortho* positions of the Ar_F ring (Scheme 2).[15,16] The nucleophilic attack at the C-iminium center that would have led to the corresponding cyclopropane **4** is probably empeded due to steric congestion. Moreover, the isomerization of **3** by 1,2-proton shift would have afforded the enamine **5**, which does not benefit in that case from any push–pull stabilization.

Notably, this dearomatizing cyclization occurs under very mild experimental conditions and proceeds with



Scheme 2. Reaction of the stable aminoarylcarbene **1** with 2-chloroacrylonitrile.

formation of a CC bond between two quaternary centers. Moreover, a single diastereomer was observed both in solution and in the solid state. It features the chlorine atom and the CF_3 group in a *trans* relationship. So far, this complete diastereoselectivity has not been rationalized.

In conclusion, the stable aminoarylcarbene **1** was found to readily add to 2-chloroacrylonitrile, affording the bicyclic compound **2** in high yield and with complete diastereoselectivity. This is a further illustration that the availability of stable carbenes allows for the observation of unusual reactions.[15] Dearomatizing cyclization[16] appears as a further competitive pathway for cyclopropanation, and the observation of cyclopropanation reactions involving a stable aminocarbene remains an exciting challenge.

Acknowledgements

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14. 2-Chloroacrylonitrile (15 μL, 0.19 mmol) was added dropwise at −78 °C to a THF solution (4 mL) of the aminoarylcarbene **1** (74 mg, 0.19 mmol). The solution was warmed to rt, and maintained at this temperature for 2 h before the solvent was removed in vacuo. The crude mixture was extracted with pentane (10 mL). The adduct **2** was obtained as colorless crystals (81 mg, 89%) from a saturated pentane solution at −30 °C. ^{19}F NMR ($CDCl_3$): δ 1.9 [s, 3F, $C(sp^3)CF_3$], 14.4 [br, 3F, $C(sp^2)CF_3$]; ^1H NMR ($CDCl_3$): δ 1.64 [m, 6H, $CH_{2(Ad)}$], 1.74 [m, 6H, $CH_{2(Ad)}$], 2.10 [m, 3H, $CH_{(Ad)}$], 2.48 (s, 3H, NCH_3), 3.19 (d, 1H, $^2J_{HH} = 17.3$ Hz, CH_2CCl), 3.55 (d, 1H, $^2J_{HH} = 17.3$ Hz, CH_2CCl), 6.11 (d, 1H, $^3J_{HH} = 9.3$ Hz, $CHCCF_3$), 6.32 (dd, 1H, $^3J_{HH} = 9.3$ and 5.7 Hz, CH), 6.48 (d, 1H, $^3J_{HH} = 5.7$ Hz, $CHCCF_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 29.8 (s, CH_{Ad}), 33.9 (s, NCH_3), 36.9 [s, $CH_{2(Ad)}$], 39.8 [s, $CH_{2(Ad)}$], 50.4 (s, C_2CCl), 55.6 (s, C_{Ad}), 123.0 [q, $^1J_{CF} = 273$ Hz, $C_3C(sp^2)$], 126.0 [q, $^1J_{CF} = 290$ Hz, $C_3C(sp^3)$], 126.6 (s, $CHCCF_3$), 127.0 (s, $CHCCF_3$), 127.4 (s, CH); MS (DCI, NH_3) 477 (MH^+), 441 [$(M-Cl)^+$], 390 [$MH-(CH_2{=}CCl(CN))]^+$. Anal. Calcd for $C_{23}H_{23}ClF_6N_2$: C 57.93, H 4.86, N 5.87; found: C 57.65, H 4.71, N 5.53. Crystallographic data (excluding structure factors) for **2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary number CCDC-232928. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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