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1,3-DIPOLAR CYCLOADDITION OF ETHYL DIAZOACETATE WITH *(E)*-3-ARYLIDENECHROMAN-4-ONES. A NEW ACCESS TO SPIRO-CYCLOPROPANE DERIVATIVES

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Abstract – *(E)*-3-Arylidenechroman-4-ones **1a–e** (Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-$MeSC_6H_4$, *p*-ClC_6H_4) react regioselectively (100%) with ethyl diazoacetate **2** in refluxing toluene to afford in good yields spiro-Δ^2-pyrazolines ethyl 4'-oxo-4-aryl-spiro[chromanone-3',5-pyrazole]-3-carboxylate **3a–e**. The occurrence of Δ^1-pyrazolines as reaction intermediates has been evidenced. The regio- and stereochemistry of spiranic compounds **3a-e** has been established on the basis of spectroscopic data and elemental analyses, corroborated by a single crystal X-ray crystallographic analysis of one product **3a**. The spiro-adducts **3a–e** were brominated by NBS to give spirocyclic-substituted 3-bromo-4,5-dihydro-3*H*-pyrazoles **4a–e**. The latter compounds evolve straightforwardly N_2 in refluxing toluene to afford substituted spirocyclic 1-bromocyclopropane-1-carboxylates. The molecular structure of cyclopropane derivative **5e** has been determined by means of a single-crystal X-ray diffraction study.

INTRODUCTION

Diazo compounds are remarkably versatile intermediates in organic synthesis that participate in a variety of thermal, photochemical, metal-catalyzed rearrangement, cycloaddition, and insertion reactions with concomitant expulsion of N_2.[1] These compounds are found in nature, examples of which include azaserine,[2] members of the kinamycin[3] and lomaiviticin[4] families of marine natural products. The high synthetic utility and pharmacological importance of ethyl diazoacetate prompted Curtius and Buchner to synthesize some biologically interesting pyrazolines derivatives.[1] The main characteristic feature of diazo esters, which is common to all aliphatic diazo compounds, is that their reactions can proceed with either retention or elimination of the diazo fragment. The 1,3-dipolar cycloaddition of diazo esters to compounds containing multiple bonds is the first step of these transformations.[5,6] The ensuing reactions with elimination of the nitrogen molecule are primarily characterized by generation of carbenes, their complexes with transition metals, cationoid reagents, and biradicals.[1,6-8]

In the case of alkenes and their derivatives, these reactions lead to the formation of 1- or 2-pyrazolines,[5] which are useful intermediates for the synthesis of various classes of compounds[9] including those possessing biological activity.[10] However, in the most cases the reactions of diazo carbonyl compounds with alkenes require long reaction times, elevated temperatures, or use of alkenes with electron-withdrawing substituents or a reactive strained double bond.

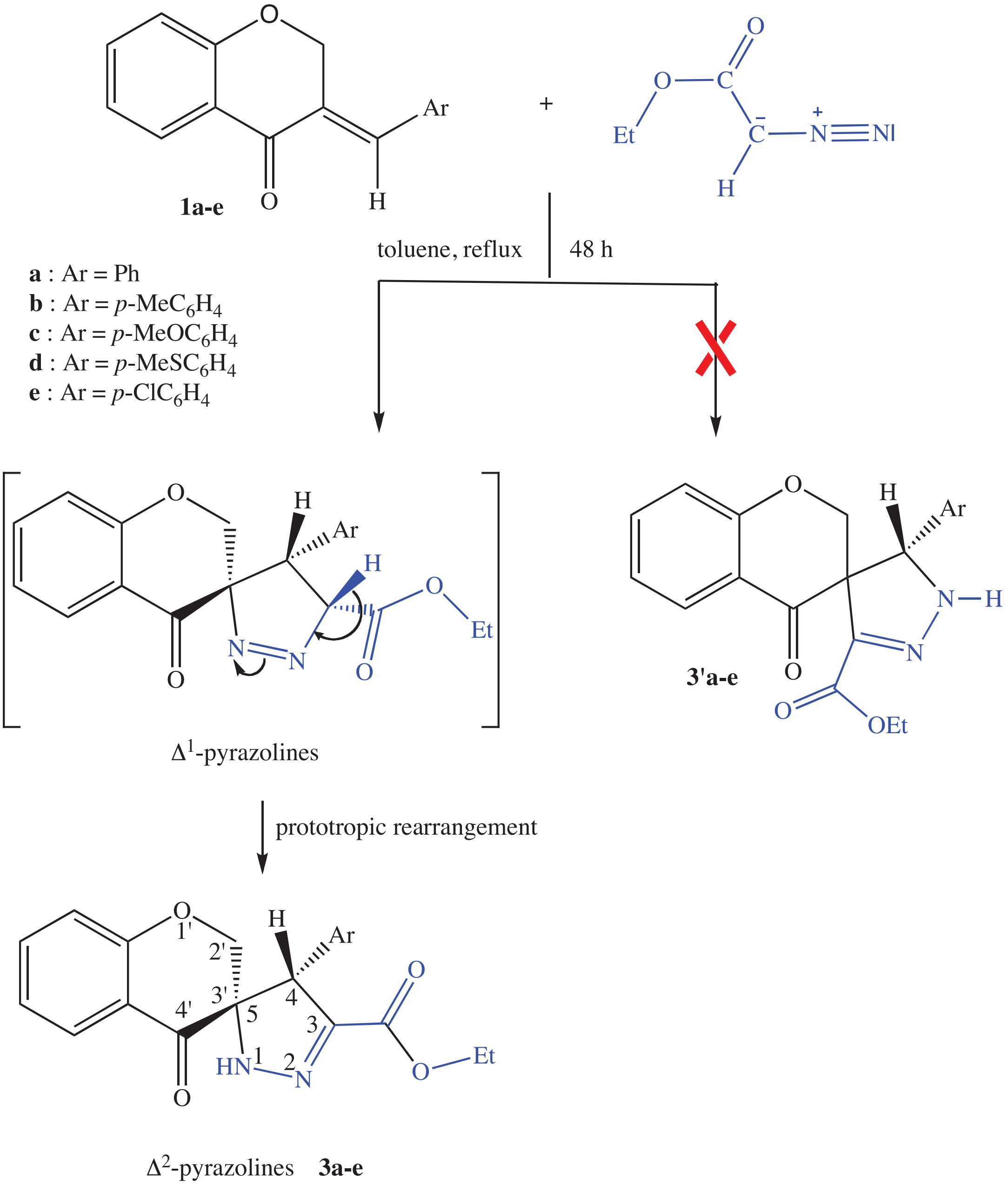
Furthermore, 4-chromanone derivatives are used as versatile intermediates for the synthesis of many natural products such as brazilin, hematoxylin, ripariochromene, clausenin, calonlide (A) and inophyllum (B).[11,12] Chromanone heterocycles have also been paid much attention owing to their important pharmacological proprieties.[13]

We have examined previously the reactivity of mono- and disubstituted diazoalkanes such as ethyl diazoacetate and diphenyldiazomethane towards α-methylene-γ-butyrolactones and itaconic anhydride.[14,15]

To the best of our knowledge, there is only one report on the cycloaddition of a diazo compounds to trisubstituted olefins, where the dipolarophiles have the reactive double bond conjugated with an aryl and a carbonyl groups.[16] Our group has also examined the reactivity of (*E*)-3-arylidenechroman-4-ones towards isoquinoline Reissert salts.[17] In continuation of our research interest in this field, we present in this contribution the first examples on the regioselective reaction of ethyl diazoacetate **2** with (*E*)-3-arylidenechroman-4-ones **1a–e**. The products **3a–e** obtained thus were transformed by action of NBS to ethyl 3-bromo-4'-oxo-4-aryl-spiro[chromanone-3',5-pyrazole]-3-carboxylate derivatives **4a–e**, which, on heating, the extrude straightforwardly N_2 with formation of cyclopropylcarboxylates **5a–e**. In order to elucidate effect of the *p*-substituent on the 3(1)-aryl group of **1** on the outcome of the reaction, we have systematically varied the electronic propensities of the substituent.

RESULTS AND DISCUSSION

The (*E*)-3-arylidenechroman-4-ones **1a–e** have been prepared by the acid-catalyzed condensation of 4-chromanones with various benzaldehydes. As confirmed by NMR spectroscopy, these starting materials had an *E*-configuration in accordance with the literature.[18-25] The 1,3-dipolar cycloaddition of **1a–e** was carried out in refluxing toluene during 48 h (Scheme 1).



Scheme 1. Cycloaddition reactions of ethyl diazoacetate **2** with (*E*)-3-arylidenechroman-4-ones **1a–e**

The dipolarophiles **1a–e** reacted with the commercially available ethyl diazoacetate **2** with the exocyclic double bond of the (*E*)-3-arylidenechroman-4-ones. In each case, only a single spiro-compound ethyl

4’-oxo-4-aryl-spiro[chromanone-3’,5-pyrazole]-3-carboxylate **3a–e** was isolated as yellow or colorless solid according to Scheme 1. The electron-rich carbon atom of the diazo compound adds to the unsaturated carbon atom β to carbonyl group. It is thus reasonable to assume that preferential approach of the dipole **2** takes place from the less-hindered diastereotopic side of the dipolarophiles **1a–e**. This reaction involves initial formation of five-membered spiranic Δ^1-pyrazoline that undergo a prototropic rearrangement to form the thermodynamically more stable Δ^2-pyrazolines, ethyl 4’-oxo-4-aryl-spiro[chromanone-3’,5-pyrazole]-3-carboxylates **3a–e**. Indeed, the formation of the intermediate five-membered spiranic Δ^1-pyrazoline was proven by a ^{1}H NMR study. When dipolarophiles **1a–e** and **2** were allowed to react for only 6 h, a mixture of Δ^1-pyrazoline and Δ^2-pyrazoline was obtained in a 40:60 ratio. After 48 h, the isomerisation of Δ^1-pyrazoline into Δ^2-pyrazoline was complete. The ^{1}H NMR spectrum of intermediate Δ^1-pyrazoline **3a** (Ar = Ph) clearly indicates the presence of two doublets around δ = 4.45 and 4.90 ppm, which correspond to protons 3-H and 4-H, respectively (Scheme 1). Furthermore, the magnitude of the vicinal coupling constant (J = 9.0 Hz) between the two protons suggests that they are in *cis*-configuration. This finding is in line with our previous observations and those reported in the literature.[14,15,26]

The structure of product **3a–e** and the regiochemistry of the cycloaddition, *i.e*. the nitrogen atom being bonded to the more substituted carbon atom of the unsymmetrical double bond, have been established on the basis of spectroscopic data and X-ray structural analysis of one cycloadduct **3a**. The IR spectra of these compounds **3a–e** contain absorption bands at 3370 cm^{-1}, 1710 cm^{-1}, 1685 cm^{-1} and 1575 cm^{-1} due to NH, ester C=O, ring C=O and C=N stretching vibrations, respectively. The ^{1}H NMR spectra display the expected triplet and quartet pattern due to the OEt group at around δ = 1.22 ppm and δ = 4.17 – 4.21 ppm, with J = 7.2 Hz. The presence of a singlet between 4.70 and 4.81 ppm, assigned to the benzylic proton 4-H, is indicative for the regiochemistry of the [3+2] cycloadition, leading exclusively to 5-spiro-fused 2-pyrazoline derivatives.[19,27-30] Two mutually coupled doublets (J = 12.3 Hz), which correspond to the methylene protons 2’-H of the chromanone ring, are observed between δ = 4.03 and 4.18 ppm. Another characteristic in products **3a–e** is the presence of a N-H proton signal between 6.57 and 6.68 ppm, exchangeable by D_2O. The ^{13}C NMR chemical shifts of the spiro-carbon atom C-5(3’), which is deshielded due to proximity of the nitrogen atom, are observed at the field between 71.56 and 71.86 ppm.[17,31] This excludes the presence of the inverse regioisomers **3’a–e**. In **3’a–e**, one should expected the resonances of theses carbons at a more upfield region than the observed experimental values.[16,32] All these data led us to conclude that the structure of adducts **3a–e** is as depicted in Scheme 1.

In the cycloadducts **3a–e** appear two new chiral centers, *i.e*. the quaternary spiro-atom C-5(3’) and the C-4 atom of pyrazoline ring (Scheme 1). The relative stereochemistry of these carbon [rel-(4S*,5(3’)R*)] results from preservation of the *(E)* configuration of the initial olefin. This stereochemistry was encountered in all cycloadducts **3a–e** and confirmed to the favored approach of the two reagents. The suggested stereochemistry of the cycloadducts was corroborated by X-ray crystal analysis of product **3a** (Figure 1). It should be noted that the phenyl group in compound **3a** is *trans*-arranged with respect to the ring carbonyl group. All metric parameters are normal and deserve no special comment. The observed regio- and stereochemistry are in accordance with previous observations by us and other investigators.[14,15,26]

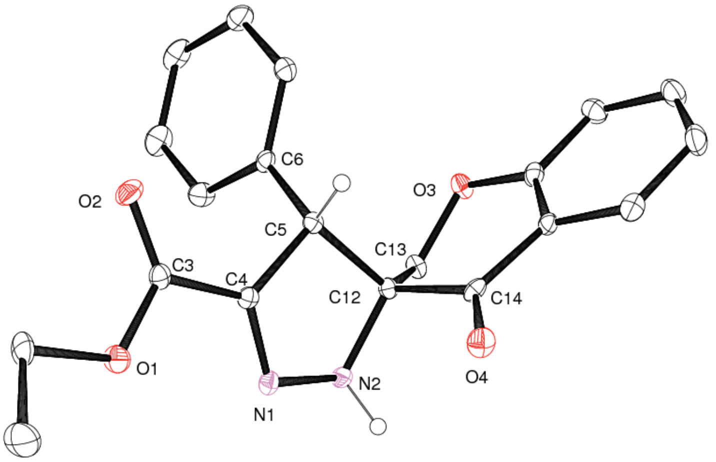
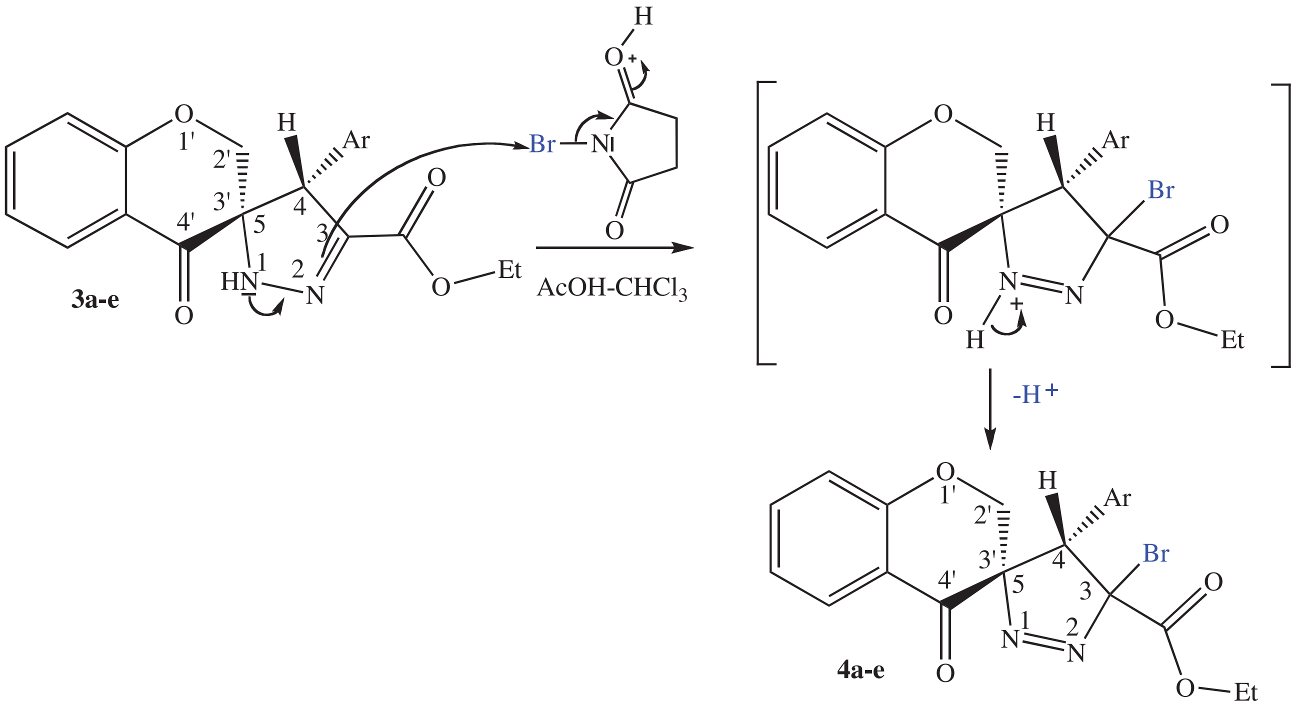


Figure 1. Molecular structure of **3a.** Selected bond lengths (Å) and angles (°). The aromatic hydrogen atoms are omitted for clarity: N1–N2 1.3604(15), N1–C4 1.2835(16), C4–C5 1.5155(17), C5–C12 1.5700(17), C12–N2 1.4659(16), C12–C13 1.5193(19), C13–O3 1.4309(15), C14–O4 1.2118(15); O1–C3–O2 124.93(13), O1–C3–C4 112.54(12), C3–C4–C5 123.61(12), C4–C5–C6 113.20(10), C4–C5–C12 98.60(10), C5–C12–C13 116.90(11), C12–C13–O3 111.81(12), C13–O3–C16 115.43(10), C5–C12–C14 108.01(11), C12–C14–O4 121.36(12), C5–C12–N2 102.15(10), C12–N2–N1 111.27(11), N2–N1–C4 108.87(11), N1–C4–C5 114.85(12)

In a next step, the Δ^2-pyrazolines **3a–e** were allowed to react at room temperature (24 h) with NBS in $CHCl_3$ solution in the presence of acetic acid. The formation of the single brominated product suggests that the reaction first involves the protonation of a carbonyl group of NBS, followed by bromination of compounds **3a–e** at the 3-position *via* an ionic process implying lone-pair participation of N-H at the 1-position to afford the corresponding Δ^1-pyrazolines ethyl-4-aryl-3-bromo-4'-oxo-spiro-[chromanone-3',5-pyrazole]-3-carboxylate **4a–e** with up to 85% yield (Scheme 2).

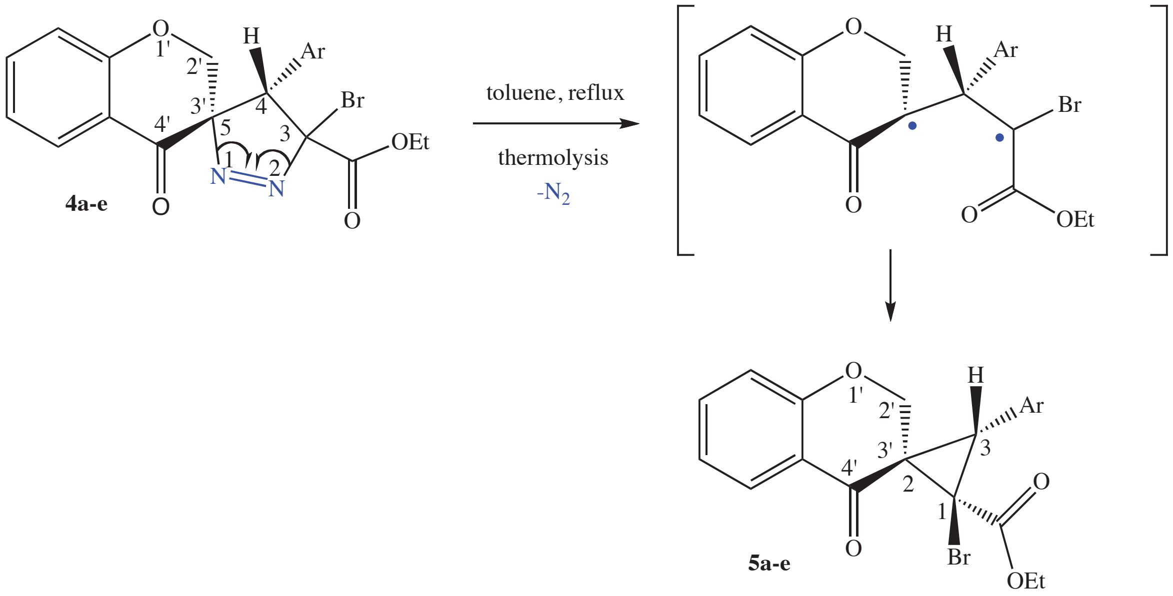
In the ^{1}H NMR spectra of these brominated products, the signal of the 4-H proton appear as a singlet in the region between 4.04-4.15 ppm. In the ^{13}C NMR spectra of esters **4a–e**, the following signals are observed, δ_c, ppm: 34.7-36.2 (4-C), 62.7-63.8 (3',5-C), 64.5-68.7 (3-C), 160.1-165.1 (C=O ester), in addition signals arising from aromatic carbon atoms are present in the spectra (see Experimental Section).



Scheme 2. NBS-bromination of **3a–e** leading to **4a–e**

It is known that thermolysis of pyrazolines may lead to formation of spiro-cyclopropane carboxylates derivatives.[33-35] Depending on the experimental conditions and the substituents at the bridgehead position, both isomers with *endo* or *exo* ester groups can be formed.[33] With this objective in mind, we have thermolyzed compounds **4a–e** in refluxing toluene for 24 h. Both spectroscopic data as well as elemental analyses were in agreement with formation of the targeted ethyl 1-bromo-3-aryl-4’-oxo-spiro [chromanone-3’,2-cyclopropane]-1-carboxylates **5a–e**. The compounds **4a–e** released N_2 generating biradicals intermediates, which then cyclize leading to the cyclopropanecarboxylates in 65-85% yield (Scheme 3). ^{1}H NMR spectra of **5a–e** confirmed the formation of single diastereoisomers during the thermal decomposition of pyrazolines **4a–e.**

In the IR spectra an absorption band at around 1710 cm^{-1} corresponding to the ester group is observed. The ^{1}H NMR spectra of **5a–e** contain a singlet in the region between 2.42-2.67 ppm arising from the cyclopropane ring proton (3-H), as well as the expected resonances of aromatic protons and those of the OEt groups. The two diastereotopic methylene protons of the six-membered cycle resonate in the range between 4.20-4.87 ppm and are mutually coupled through a ^{2}J coupling of 12.3 Hz. Compounds **5a–e** display the following signals in the ^{13}C NMR spectra, δ_c, ppm: 32.4-35.9 (3-C), 62.6-63.7 (3’,2-C), 62.3-65.4 (1-C). Signals of the carbon atoms within the cyclopropane ring appeared upfield-shifted relative to those belonging to the pyrazoline ring carbon atoms of the precursor compounds **4**.



Scheme 3. stereospecific thermolysis of **4a–e** producing spiro-cyclopropanecarboxylates **5a–e**

Furthermore, formation of a spirocyclic cyclopropane derivative has been confirmed by an X-ray crystal structure determination of **5e** (Figure 2). Each carbon atom of the cyclopropane ring of **5e** is chiral, formally giving rise to several diastereoisomers. However, there is only one molecule of **5e** in the asymmetric unit of P-1 triclinic centrosymmetric space group, indicating that only one pair of enantiomers is present in the crystal. These are the 8*R*, 10*R*, 11*S* and 8*S*, 10*S*, 11*R* on C8, C10 and C11 atoms. Such a natural choice of an enantiomeric pair may be attributed to the relatively low molecular energy when the O1, Br and the H atom bound to C10 (see Figure 2) are placed over the same face of the cyclopropane ring, thus reducing the steric hindrances. All metric parameters are normal and deserve no further comment.

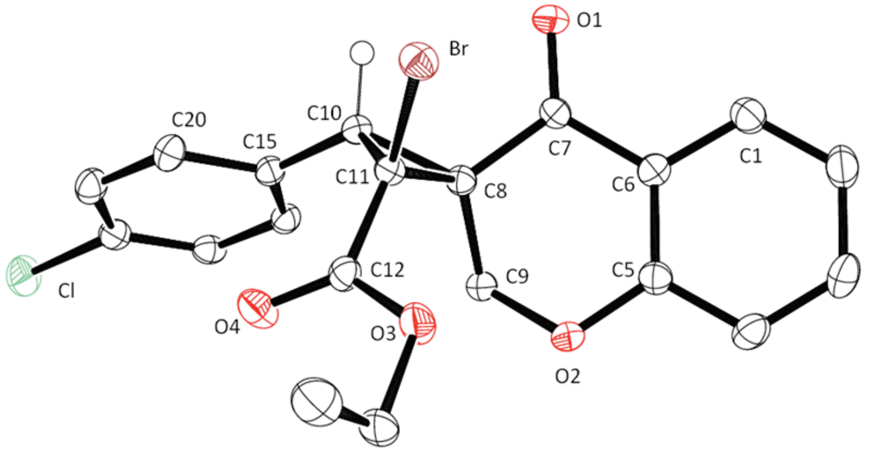


Figure 2. Molecular structure of **5e**. Selected bond lengths (Å) and angles (°): C8–C10 1.516(3), C8–C11 1.532(3), C10–C11 1.504(3), C11–Br 1.928(2), C8–C10–C11 60.9(1), C10–C11–C8 59.9(1), C10–C8–C11 59.1(1), C7–C8–C9 111.6(2)

CONCLUSION

We have shown that the reaction of ethyl diazoacetate **2** with (*E*)-3-arylidenechroman-4-ones **1a–e** is regio- and stereoselective. Independently of the electronic nature of the *p*-substituents on the 3(1)-aryl group of dipolarophiles **1a–e**, the electron-rich carbon atom of the diazo compound **2** added to the unsaturated carbon atom β to carbonyl group. The observed regioselectivity is thus in accordance with other previous studies of our research groups. Spiro esters **3a–e** react under mild conditions with NBS in $CHCl_3$ solution in the presence of acetic acid to afford ethyl 3-bromo-4'-oxo-4-aryl-spiro[chromanone-3',5-pyrazole]-3-carboxylates **4a–e.** Subsequent thermolysis of **4a–e** in refluxing toluene leads under N_2-extrusion in a stereoselective manner to the cyclopropanecarboxylate derivatives **5a–e** which have an *exo*-configuration of the ester group. Currently, complementary studies on the cycloaddition of ethyl diazoacetate with (*Z*)-3-arylidene-2(*3H*)benzofuranones and 2-arylideneindan-1,3- diones are underway.

EXPERIMENTAL

General Remarks: Reactions were carried out under an atmosphere of dry N_2. Solvents were purified by standard methods and freshly distilled under nitrogen and dried before use. Melting points were determined on a Kofler bank. IR spectra were recorded in KBr pellets on a Perkin-Elmer 197 spectrometer; only structurally significant bands are reported. NMR spectra were recorded with a Bruker-Spectrospin AC 300 spectrometer operating at 300 MHz for ^1H and 75.5 MHz for ^{13}C using TMS as internal standard (0.00 ppm) in $CDCl_3$ as solvent. Chemical shifts were reported in ppm (δ) downfield from TMS. (*E*)-3-arylidenechroman-4-ones **1a–e** were obtained by aldol condensation of arylaldehydes ArCHO with the respective chromanones according to reported methods.[18-25] Ethyl diazoacetate **2** was purchased from Aldrich.

General procedure for the preparation of the cycloadducts (3a–e)

A solution of dipolarophiles **1a**–**e** (1 mmol) and ethyl diazoacetate (1 mmol) **2** in dry toluene (10 mL) was stirred under reflux for 48 h. Then the solvent was evaporated under reduced pressure and the residue was recrystallized from EtOH to afford compounds **3a**–**e**.

Ethyl 4'-oxo-4-phenyl-spiro[chromanone-3',5-pyrazole]-3-carboxylate 3a

Yield 0.26 g (75%); colorless solid; mp 176 °C; IR (KBr, cm^{-1}): 3290 (N-H), 1710 (C=O ester), 1685 (C=O), 1570 (C=N); ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H, J = 7.2 Hz, CH_3); 4.03 (d, 1H, J = 12.3 Hz, 2'-H); 4.14 (d, 1H, J = 12.3 Hz, 2'-H); 4.21 (q, 2H, J = 7.2 Hz, CH_2-O); 4.81 (s, 1H, 4-H); 6.64 (s, 1H, N-H); 6.91-7.97 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3); 54.2 (4-C); 61.4 (2'-C); 69.7 (CH_2-O); 71.5 (3',5-C); 117.9-146.6 (aromatic C); 160.8 (C=N); 161.2 (C=O ester); 189.5 (4'-C=O). Anal. Calcd for

$C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.49; H, 5.09; N, 7.94.

Ethyl 4'-oxo-4-(*p*-tolyl)-spiro[chromanone-3',5-pyrazole]-3-carboxylate 3b

Yield 0.22 g (60%); yellow solid; mp 178 °C; IR (KBr, cm^{-1}): 3280 (N-H), 1712 (C=O ester), 1686 (C=O), 1550 (C=N); ^1H NMR ($CDCl_3$): δ 1.22 (t, 3H, *J* = 7.2 Hz, CH_3); 1.56 (s, 3H, CH_3) ; 4.05 (d, 1H, *J* = 12.3 Hz, 2'-H); 4.15 (d, 1H, *J* = 12.3 Hz, 2'-H); 4.18 (q, 2H, *J* = 7.2 Hz, CH_2-O); 4.76 (s, 1H, 4-H); 6.57 (s, 1H, N-H) ; 6.92-7.97 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_3); 21.6 (CH_3); 54.3 (4-C); 61.7 (2'-C); 70.0 (CH_2-O); 71.8 (3',5-C); 118.2-147.2 (aromatic C); 161.2 (C=N); 161.5 (C=O ester); 190.1 (4'-C=O). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.15; H, 5.43; N, 7.61.

Ethyl 4'-oxo-4-(*p*-anisyl)-spiro[chromanone-3',5-pyrazole]-3-carboxylate 3c

Yield 0.31 g (82%); yellow solid; mp 142 °C; IR (KBr, cm^{-1}): 3289 (N-H), 1710 (C=O ester), 1684 (C=O), 1570 (C=N); ^1H NMR ($CDCl_3$): δ 1.22 (t, 3H, *J* = 7.2 Hz, CH_3); 4.06 (d, 1H, *J* = 12.0 Hz, 2'-H); 4.16 (d, 1H, *J* = 12.0 Hz, 2'-H); 4.17 (q, 2H, *J* = 7.2 Hz, CH_2-O); 3.86 (s, 3H, OCH_3) ; 4.70 (s, 1H, 4-H); 6.50 (s, 1H, N-H) ; 6.95-8.03 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3); 54.2 (4-C); 55.2 (OCH_3); 61.4 (2'-C); 69.7 (CH_2-O); 71.6 (3',5-C); 117.9-146.4 (aromatic C); 160.8 (C=N); 161.2 (C=O ester); 189.5 (4'-C=O). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.19; H, 5.35; N, 7.29.

Ethyl 4'-oxo-4-(*p*-methylthiophenyl)-spiro[chromanone-3',5-pyrazole]-3-carboxylate 3d

Yield 0.33 g (85%); colorless solid; mp 168 °C; IR (KBr, cm^{-1}): 3270 (N-H), 1711 (C=O ester), 1684 (C=O), 1560 (C=N); ^1H NMR ($CDCl_3$): δ 1.22 (t, 3H, *J* = 7.2 Hz, CH_3); 2.48 (s, 3H, SCH_3); 4.06 (d, 1H, *J* = 12.0 Hz, 2'-H); 4.18 (d, 1H, *J* = 12.0 Hz, 2'-H); 4.21 (q, 2H, *J* = 7.2 Hz, CH_2-O); 4.73 (s, 1H, 4-H); 6.64 (s, 1H, N-H) ; 6.91-7.93 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3); 15.4 (SCH_3); 53.8 (4-C); 61.4 (2'-C); 69.5 (CH_2-O); 71.5 (3',5-C); 117.7-146.4 (aromatic C); 160.7 (C=N); 161.1 (C=O ester); 189.6 (4'-C=O). Anal. Calcd for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.08; N, 7.07. Found: C, 63.51; H, 5.02; N, 7.01.

Ethyl 4'-oxo-4-(*p*-chlorophenyl)-spiro[chromanone-3',5-pyrazole]-3-carboxylate 3e

Yield 0.33 g (87%); colorless solid; mp 166 °C; IR (KBr, cm^{-1}): 3280 (N-H), 1710 (C=O ester), 1683 (C=O), 1570 (C=N); ^1H NMR ($CDCl_3$): δ 1.24 (t, 3H, *J* = 7.2 Hz, CH_3); 4.03 (d, 1H, *J* = 12.3 Hz, 2'-H); 4.16 (d, 1H, *J* = 12.3 Hz, 2'-H); 4.19 (q, 2H, *J* = 7.2 Hz, CH_2-O); 4.74 (s, 1H, 4-H); 6.68 (s, 1H, N-H); 6.92-7.96 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3); 53.7 (4-C); 61.5 (2'-C); 69.2 (CH_2-O); 71.6

(3’,5-C); 117.8-146.2 (aromatic C); 160.2 (C=N); 161.0 (C=O ester); 189.3 (4’-C=O). Anal. Calcd for $C_{20}H_{17}ClN_2O_4$: C, 62.42; H, 4.45; N, 7.28. Found: C, 62.30; H, 4.38; N, 7.23.

***General procedure for the preparation of compounds* (4a–e)**

N-Bromosuccinimide, (1.1 mmol), was added at room temperature to a solution of 1 mmol of **3a–e** in a mixture of 20 mL of anhydrous $CHCl_3$ and 10 mL of acetic acid. When the reaction was complete (TLC), the mixture was stirred for an additional 40 min and washed with water, a 5% aqueous solution of sodium hydrogen carbonate, and water again. The organic phase was dried over $MgSO_4$, evaporated to a volume of ca. 5 mL, diluted with 10 mL of EtOH, evaporated again, and the precipitate was filtered.

Ethyl 3-bromo-4’-oxo-4-phenyl-spiro[chromanone-3’,5-pyrazole]-3-carboxylate 4a

Yield 0.30 g (70%); colorless solid; mp 154 °C; IR (KBr, cm^{-1}): 800 (C-Br), 1300 (C-N), 1710 (C=O ester); 1684 (C=O); ^1H NMR ($CDCl_3$): δ 0.91 (t, 3H, *J* = 7.3 Hz, CH_3); 4.15 (s, 1H, 4-H); 4.23 (q, 2H, *J* = 7.3 Hz, CH_2-O); 4.53 (d, 1H, *J* = 12.3 Hz, 2’-H); 4.58 (d, 1H, *J* = 12.3 Hz, 2’-H); 6.92-8.04 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 12.9 (CH_3); 35.6 (4-C); 36.9 (2’-C); 50.1 (CH_2-O); 63.8 (3’,5-C); 68.7 (3-C); 126.0-155.3 (aromatic C); 160.1 (C=O ester); 188.4 (4’-C=O). Anal. Calcd for $C_{20}H_{17}BrN_2O_4$: C, 55.96; H, 3.99; N, 6.53. Found: C, 55.89; H, 3.90; N, 6.46.

Ethyl 3-bromo-4’-oxo-4-(*p*-tolyl)-spiro[chromanone-3’,5-pyrazole]-3-carboxylate 4b

Yield 0.24 g (54%); yellow solid; mp 160 °C; IR (KBr, cm^{-1}): 815 (C-Br), 1310 (C-N), 1711 (C=O ester); 1685 (C=O); ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H, *J* = 7.3 Hz, CH_3); 1.54 (s, 3H, CH_3) ; 4.04 (s, 1H, 4-H); 4.20 (q, 2H, *J* = 7.3 Hz, CH_2-O); 4.72 (d, 1H, *J* = 12.3 Hz, 2’-H); 4.83 (d, 1H, *J* = 12.3 Hz, 2’-H); 6.98-8.06 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 13.9 (CH_3); 20.5 (CH_3); 36.2 (4-C); 37.4 (2’-C); 51.2 (CH_2-O); 62.7 (3’,5-C); 64.5 (3-C); 117.3-145.2 (aromatic C); 162.4 (C=O ester); 189.4 (4’-C=O). Anal. Calcd for $C_{21}H_{19}BrN_2O_4$: C, 56.90; H, 4.32; N, 6.32. Found: C, 56.81; H, 4.22; N, 6.24.

Ethyl 3-bromo-4’-oxo-4-(*p*-anisyl)-spiro[chromanone-3’,5-pyrazole]-3-carboxylate 4c

Yield 0.39 g (80%); yellow solid; mp 135 °C; IR (KBr, cm^{-1}): 820 (C-Br), 1315 (C-N), 1712 (C=O ester); 1684 (C=O); ^1H NMR ($CDCl_3$): δ 1.18 (t, 3H, *J* = 7.3 Hz, CH_3); 3.86 (s, 3H, OCH_3); 4.11 (s, 1H, 4-H); 4.21 (q, 2H, *J* = 7.3 Hz, CH_2-O); 4.65 (d, 1H, *J* = 12.3 Hz, 2’-H); 4.80 (d, 1H, *J* = 12.3 Hz, 2’-H); 7.03-8.05 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 13.6 (CH_3); 34.7 (4-C); 38.3 (2’-C); 44.7 (CH_2-O); 55.1 (CH_3-O); 65.5 (3’,5-C); 66.4 (3-C); 118.2-148.3 (aromatic C); 163.1 (C=O ester); 187.5 (4’-C=O). Anal. Calcd for $C_{21}H_{19}BrN_2O_5$: C, 54.92; H, 4.17; N, 6.10. Found: C, 54.88; H, 4.21; N, 6.17.

Ethyl 3-bromo-4'-oxo-4-(*p*-methylthiophenyl)-spiro[chromanone-3',5-pyrazole]-3-carboxylate 4d

Yield 0.35 g (75%); colorless solid; mp 150 °C; IR (KBr, cm^{-1}): 810 (C-Br), 1300 (C-N), 1710 (C=O ester); 1683 (C=O); ^1H NMR ($CDCl_3$): δ 1.16 (t, 3H, J = 7.3 Hz, CH_3); 2.41 (s, 3H, SCH_3); 4.09 (s, 1H, 4-H); 4.22 (q, 2H, J = 7.3 Hz, CH_2-O); 4.67 (d, 1H, J = 12.0 Hz, 2'-H); 4.82 (d, 1H, J = 12.0 Hz, 2'-H); 6.98-8.02 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 12.7 (CH_3); 14.2 (SCH_3); 35.3 (4-C); 37.3 (2'-C); 50.2 (CH_2-O); 64.6 (3',5-C); 65.8 (3-C) ; 125.3-145.5 (aromatic C); 165.0 (C=O ester); 187.5 (4'-C=O). Anal. Calcd for $C_{21}H_{19}BrN_2O_4S$: C, 53.06; H, 4.03; N, 5.89. Found: C, 53.00; H, 3.98; N, 5.81.

Ethyl 3-bromo-4'-oxo-4-(*p*-chlorophenyl)-spiro[chromanone-3',5-pyrazole]-3-carboxylate 4e

Yield 0.39 g (85%); colorless solid; mp 140 °C; IR (KBr, cm^{-1}): 813 (C-Br), 1311 (C-N), 1709 (C=O ester); 1685 (C=O); ^1H NMR ($CDCl_3$): δ 1.23 (t, 3H, J = 7.3 Hz, CH_3); 4.08 (s, 1H, 4-H); 4.20 (q, 2H, J = 7.3 Hz, CH_2-O); 4.78 (d, 1H, J = 12.3 Hz, 2'-H); 4.87 (d, 1H, J = 12.3 Hz, 2'-H); 7.03-8.04 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3); 35.9 (4-C); 38.5 (2'-C); 41.2 (CH_2-O); 63.1 (3',5-C); 66.8 (3-C); 118.2-136.6 (aromatic C); 165.1 (C=O ester); 186.1 (4'-C=O). Anal. Calcd for $C_{20}H_{16}BrClN_2O_4$: C, 51.80; H, 3.48; N, 6.04. Found: C, 51.71; H, 3.42; N, 5.90.

***General procedure for the preparation of the ethyl cyclopropanecarboxylates* (5a–e)**

A solution of 0.3 mmol of **4a–e** in 4 mL of toluene was refluxed for 24 h (TLC), until evolution of nitrogen stopped. The solvent was then evaporated, 2 mL of EtOH were added to the residue, and the formed precipitates were filtered and recrystallized from EtOH.

Ethyl 1-bromo-3-phenyl-4'-oxo-spiro[chromanone-3',2-cyclopropane]-1-carboxylate 5a

Yield 0.10 g (80%); colorless solid; mp 110 °C; IR (KBr, cm^{-1}): 805 (C-Br), 1710 (C=O ester); 1686 (C=O), ^1H NMR ($CDCl_3$): δ 0.64 (t, 3H, J = 7.3 Hz, CH_3); 2.67 (s, 1H, 3-H); 3.78 (q, 2H, J = 7.3 Hz, CH_2-O); 4.20 (d, 1H, J = 12.3 Hz, 2'-H); 4.57 (d, 1H, J = 12.3 Hz, 2'-H); 6.79-8.02 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 12.7 (CH_3); 34.5 (3-C); 36.7 (2'-C); 49.8 (CH_2-O); 63.7 (3',2-C); 65.4 (1-C); 117.6-146.4 (aromatic C); 160.0 (C=O ester); 187.3 (4'-C=O). Anal. Calcd for $C_{20}H_{17}BrO_4$: C, 59.87; H, 4.27. Found: C, 59.80; H, 4.20.

Ethyl 1-bromo-3-(*p*-tolyl)-4'-oxo-spiro[chromanone-3',2-cyclopropane]-1-carboxylate 5b

Yield 0.09 g (77%); yellow solid; mp 120 °C; IR (KBr, cm^{-1}): 810 (C-Br), 1712 (C=O ester); 1684 (C=O); ^1H NMR ($CDCl_3$): δ 0.73 (t, 3H, J = 7.3 Hz, CH_3); 1.56 (s, 3H, CH_3); 2.56 (s, 1H, 3-H); 3.73 (q, 2H, J = 7.3 Hz, CH_2-O); 4.41 (d, 1H, J = 12.3 Hz, 2'-H); 4.80 (d, 1H, J = 12.3 Hz, 2'-H); 6.83-7.93 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 13.6 (CH$_3$); 20.4 (CH$_3$); 35.9 (3-C); 37.2 (2'-C); 50.9 (CH$_2$-O); 62.3 (1-C); 62.6 (3',2-C); 118.1-146.9 (aromatic C); 161.2 (C=O ester); 189.4 (4'-C=O). Anal. Calcd for $C_{21}H_{19}BrO_4$: C, 60.74; H, 4.61. Found: C, 60.61; H, 4.75.

Ethyl 1-bromo-3-(*p*-anisyl)-4'-oxo-spiro[chromanone-3',2-cyclopropane]-1-carboxylate 5c

Yield 0.08 g (65%); yellow solid; mp 95 °C; IR (KBr, cm^{-1}): 815 (C-Br), 1711 (C=O ester); 1684 (C=O); ^{1}H NMR (CDCl$_3$): δ 0.78 (t, 3H, *J* = 7.3 Hz, CH$_3$); 2.60 (s, 1H, 3-H); 3.75 (q, 2H, *J* = 7.3 Hz, CH$_2$-O); 3.83 (s, 3H, OCH$_3$); 4.62 (d, 1H, *J* = 12.3 Hz, 2'-H); 4.78 (d, 1H, *J* = 12.3 Hz, 2'-H); 6.91-7.78 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 13.4 (CH$_3$); 32.7 (3-C); 37.8 (2'-C); 43.6 (CH$_2$-O); 55.1 (CH$_3$-O); 64.5 (3',2-C); 64.7 (1-C); 117.4-146.3 (aromatic C); 160.9 (C=O ester); 189.3 (4'-C=O). Anal. Calcd for $C_{21}H_{19}BrO_5$: C, 58.48; H, 4.44. Found: C, 58.40; H, 4.53.

Ethyl 1-bromo-3-(*p*-methylthiophenyl)-4'-oxo-spiro[chromanone-3',2-cyclopropane]-1-carboxylate 5d

Yield 0.11 g (85%); colorless solid; mp 114 °C; IR (KBr, cm^{-1}): 800 (C-Br), 1711 (C=O ester); 1684 (C=O); ^{1}H NMR (CDCl$_3$): δ 0.67 (t, 3H, *J* = 7.3 Hz, CH$_3$); 2.35 (s, 3H, SCH$_3$); 2.64 (s, 1H, 3-H); 3.77 (q, 2H, *J* = 7.3 Hz, CH$_2$-O); 4.46 (d, 1H, *J* = 12.3 Hz, 2'-H); 4.80 (d, 1H, *J* = 12.3 Hz, 2'-H); 6.95-7.75 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 12.4 (CH$_3$); 14.1 (SCH$_3$); 34.9 (3-C); 37.1 (2'-C); 49.7 (CH$_2$-O); 63.5 (3',2-C); 64.6 (1-C); 117.5-144.2 (aromatic C); 164.8 (C=O ester); 185.6 (4'-C=O). Anal. Calcd for $C_{21}H_{19}BrO_4S$: C, 56.38; H, 4.28. Found: C, 56.30; H, 4.18.

Ethyl 1-bromo-3-(*p*-chlorophenyl)-4'-oxo-spiro[chromanone-3',2-cyclopropane]-1-carboxylate 5e

Yield 0.10 g (80%); colorless solid; mp 112 °C; IR (KBr, cm^{-1}): 812 (C-Br), 1710 (C=O ester); ^{1}H NMR (CDCl$_3$): δ 0.81 (t, 3H, *J* = 7.3 Hz, CH$_3$); 2.42 (s, 1H, 3-H); 3.83 (q, 2H, *J* = 7.3 Hz, CH$_2$-O); 4.48 (d, 1H, *J* = 12.3 Hz, 2'-H); 4.87 (d, 1H, *J* = 12.3 Hz, 2'-H); 6.81-7.85 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 13.5 (CH$_3$); 35.4 (3-C); 37.9 (2'-C); 40.8 (CH$_2$-O); 62.8 (3',2-C); 65.4 (1-C); 117.8-135.4 (aromatic C); 164.7 (C=O ester); 185.42 (4'-C=O). Anal. Calcd for $C_{20}H_{16}BrClO_4$: C, 55.13; H, 3.70. Found: C, 55.08; H, 3.65.

X-Ray structure analyses of 3a and 5e.

Intensity data for **3a** were collected on a Brucker AXS diffractometer with MoKα radiation. The crystal structure was solved by direct methods (SHELXS)[36] and refined (SHELXL)[36] with full-matrix least squares on F^2. X-Ray intensity data for **5e** were collected at 115 K with MoKα radiation on a Nonius

Kappa Apex II diffractometer. The crystal structure was solved by direct methods[37] and refined with full-matrix least squares on F^2.[37,38] Anisotropic thermal parameters were applied for non-hydrogen atoms. All H atoms were placed in calculated positions and included in final refinements with isotropic temperature factors in a riding model on the carbon atoms bearing them.

Crystal data for **3a**: $C_{20}H_{18}N_2O_4$, M = 350.36, monoclinic, space group $P2_1/c$, a = 7.1947(3) Å, b = 17.1869(7) Å, c = 13.6470(7) Å, β = 90.803(4)°, V = 1687.34(13) Å^3, Z = 4, D_c = 1.379 Mg/m^3, λ(Mo-Kα) = 0.71073 Å, F(000) = 736, μ(Mo-Kα) = 0.097 mm^{-1}, T = 173(2) K. 11957 reflections collected, 3312 unique (R_{int} = 0.0331) and 2253 with $I>2\sigma(I)$. Final residuals ρ_{max} = 0.211, ρ_{min} = -0.231 e$^-$/Å^3. Final agreement factors: $R(F)$ = 0.0343 and 0.0572, $wR(F2)$ = 0.0620 and 0.0638 for $I>2\sigma(I)$ and all data, respectively, GOF = 1.067.

Crystal data for **5e**: $C_{20}H_{16}BrClO_4$: M = 435.69, triclinic, space group P-1, a = 6.5526(2) Å, b = 10.1940(4) Å, c = 13.3432(6) Å, α = 86.801(2), β = 85.906(2), γ = 86.323(2)°, V = 886.01(6) Å^3, Z = 2, λ(Mo-Kα) = 0.71073 Å, F(000) = 440, μ(Mo-Kα) = 2.494 mm^{-1}, D_{calc} = 1.633 g/cm^3, T = 115(2) K. 7650 reflections collected, 4074 unique (R_{int} = 0.0252) and 3708 with $I>2\sigma(I)$. Final agreement factors: $R(F)$ = 0.0330 and 0.0395 and $wR(F2)$ = 0.0729 and 0.777 for $I>2\sigma(I)$ and all data, respectively, GOF = 1.120. Final residuals ρ_{max} = 0.416, ρ_{min} = -0.366 e$^-$/Å^3.

Crystallographic data for the structures of **3a** and **5e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 854948 and 854949. Copy of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK, fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

REFERENCES AND NOTES

1. M. Regitz and G. Maas, Diazo Compounds: Properties and Synthesis, *Academic Press,* Orlando, Florida, 1986, 65; A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223; M. P. Doyle, M. A. McKervey, and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley and Sons: New York, 1998; H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861; Z. Zhang and J. Wang, *Tetrahedron,* 2008, **64**, 6577.
2. Q. R. Bartz, C. C. Elder, R. P. Frohardt, S. A. Fusari, T. H. Haskell, D. W. Johannessen, and A. Ryder, *Nature,* 1954, **173**, 72.
3. S. Ito, T. Matsuya, S. Omura, M. Otani, A. Nakagawa, H. Takeshima, Y. Iwai, M. Ohtani, and T. Hata, *J. Antibiot.*, 1970, **23**, 315; S. J. Gould, N. Tamayo, C. R. Melville, and M. C. Cone, *J. Am. Chem. Soc.*, 1994, **116**, 2207; S. Mithani, G. Weeratunga, N. J. Taylor, and G. I. Dmitrienko, *J. Am. Chem. Soc.*, 1994, **116**, 2209.

4. H. He, W. D. Ding, V. S. Bernan, A. D. Richardson, C. M. Ireland, M. Greenstein, G. A. Ellestad, and G. T. Carter, *J. Am. Chem. Soc.*, 2001, **123**, 5362.
5. M. Regitz and H. Heydt, *1,3-Cycloaddition Chemistry*, ed. by A. Padwa, John Wiley and Sons, New York, 1984, **1**, 394.
6. E. A. Shapiro, A. B. Dyatkin, and O. M. Nefedov, *Diazoesters*, Nauka, Moscow, 1992, 148.
7. G. Maas, *Topics in Current Chemistry*, Springer-Verlag, Berlin, 1987, **137**, 75.
8. M. P. Doyle, *Chem. Rev.*, 1986, **86**, 919.
9. G. Maas, in *The Chemistry of Heterocyclic Compounds*; Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products, ed. by A. Padwa and W. H. Pearson, John Wiley and Sons, New York, 2002, **59**, 539.
10. T. Kano, T. Hashimoto, and K. Maruoka, *J. Am. Chem. Soc.*, 2006, **128**, 2174.
11. E. E. Schweizer and D. Meeder-Nycz, *in Chromenes, Chromanones, and Chromones,* ed. by G. P. Ellis, John Wiley and Sons, New York, 1977, 70; I. M. Lockhart, *in Chromenes, Chromanones, and Chromones,* ed. by G. P. Ellis, John Wiley and Sons, New York, 1977, 301.
12. B. Chenera, M. L. West, J. A. Finkelstein, and G. B. J. Dreyer, *J. Org. Chem.*, 1993, **58**, 5605.
13. A. F. Crowther, R. Howe, B. J. McLoughlin, K. B. Mallion, B. S. Rao, L. H. Smith, and R. W. Turner, *J. Med. Chem.*, 1972, **15**, 260.
14. C. Roussel, K. Ciamala, J. Vebrel, J. M. Melot, J. Vebrel, and C. Riche, *J. Chem. Res. (S),* 2002, 449.
15. C. Roussel, K. Ciamala, J. Vebrel, M. Knorr, and M. M. Kubicki, *Heterocycles*, 2007, **71**, 1517.
16. A. P. Molchanov, V. S. Korotkov, and R. R. Kostikov, *Russ. J. Org. Chem.*, 2004, **40**, 470.
17. M. Askri, M. Rammah, K. Monnier-Jobé, K. Ciamala, M. Knorr, and C. Strohmann, *Lett. Org. Chem.,* 2007, **4**, 146.
18. B. Bennet, J. A. Donnelly, D. C. Meaney, and P. O. Boyle, *J. Chem. Soc., Perkin Trans 1*, 1972, 1554.
19. R. Raghunathan, M. Shanmugasundaram, S. Bhanumathi, and E. J. Padma Malar, *Heteroatom Chem.*, 1998, **9**, 327.
20. N. K. Sangwan and S. N. Rastogi, *Indian J. Chem.*, 1981, **20B**, 135.
21. G. Wagner, C. Garbe, H. Vieweg, M. Brunn, and A. Dittrich, *Pharmazie*, 1979, **34**, 55.
22. G. C. Wright, *J. Heterocycl. Chem.,* 1976, **13**, 1177.
23. J. N. Chatterjea, S. C. L. Shaw, P. K. Lal, and R. P. Singh, *J. Indian Chem. Soc.,* 1979, **56**, 1006.
24. D. Basavaiah, M. Bakthadoss, and S. Pandiaraju, *J. Chem. Soc., Chem. Commun.*, 1998, **16**, 1639.
25. S. Manikandan, M. Shanmugasundaram, R. Raghunathan, and E. J. Padmar Malar, *Heterocycles*, 2000, **53**, 579.

26. V. M. Berestovitskaya, N. A. Anisimova, A. T. Gubaidullin, I. A. Litvinov, G. A. Berkova, and N. G. Makarova, *Russ. J. General Chem.*, 2009, **79**, 1446.

27. R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, 1962, **17**, 3.

28. R. Huisgen, *Bull. Soc. Chim. Fr.*, 1965, 3431.

29. G. Bianchi, R. Gandolfi, and C. De Micheli, *J. Chem. Res.* (*S*), 6 and (*M*), 1981, 135.

30. K. N. Houk and Y. Yamaguchi, *Theory of 1,3-Dipolar Cycloadditions in 1,3-Dipolar Cycloaddition Chemistry,* ed. by A. Padwa, John Wiley and Sons, 1984, **2**, 407.

31. R. Fihi, K. Ciamala, J. Vebrel, and N. Rodier, *Bull. Soc. Chim. Belg.,* 1995, **104**, 55.

32. M. M. Rammah, M. Othman, K. Ciamala, C. Strohmann, and M. B. Rammah, *Tetrahedron*, 2008, **64**, 3505.

33. S. A. Molchanov, A. V. Stepakov, and R. R. Kostikov, *Russ. J. Org. Chem.*, 2000, **36**, 899.

34. G. Mass, in *Methods of Organic Chemistry*, ed. by A. de Meijere, Georg Thieme, 1997, **17a**, 405.

35. R. J. Buschby, *Methoden der Organischen Chemie* (Houben-Weyl), ed. by A. de Meijere, Stuttgart: Georg Thieme 4th Ed. 1997, **E17b**, 1059.

36. SIR92 program, A. Altomare, G. Cascarano, C. Giacovazzo, and A. Guagliardi, *J. Appl. Crystallogr.*, 1993, **32**, 115.

37. G. M. Sheldrick, *Acta Cryst.,* 2008, **A64**, 112.

38. SUPERFLIP program, L. Palatinus and G. Chapuis, *J. Appl. Crystallogr.,* 2007, **40**, 786.