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Nucleophilicities of Cyclic α-Diazo Carbonyl Compounds

Le Li,[a] Jer-Ray Hsu,[a] Hongqing Zhao,[a] and Armin R. Ofial*[a]

The one-bond nucleophilic reactivities of seven cyclic α-diazo carbonyl compounds in dichloromethane were determined by analyzing the kinetics of their reactions with benzhydrylium ions (one-bond reference electrophiles) at 20 °C according to the Mayr-Patz equation. Though not calibrated for pericyclic reactions, the identified nucleophilicities also reflect relative reactivities of the α-diazo carbonyl compounds in 1,3-dipolar cycloadditions with dimethyl acetylenedicarboxylate. These (3 + 2)-cycloadditions primarily gave spirocyclic 3*H*-pyrazoles, which underwent thermal [1,5]-sigmatropic (van Alphen-Hüttel) rearrangements to furnish 1*H*-pyrazole-fused tricyclic products.

Introduction

Diazoalkanes ($RR'C{=}N_2$) are ambiphilic reagents. On one hand, they react with electrophiles at the carbon atom of the diazo unit to yield diazonium ions. On the other hand, attack of nucleophiles at the terminal nitrogen of diazoalkanes furnishes azo compounds (Figure 1a).[1] Currently, Mayr's reactivity scales constitute the most comprehensive framework for the semi-quantitative calibration of such nucleophilic and electrophilic reactivities, respectively.[2]

$$\lg k_2(20\,^{\circ}\mathrm{C}) = s_N(N + E) \qquad (1)$$

Based on the correlation equation (1), one-bond electrophilicities are expressed by the descriptor *E* and solvent-dependent one-bond nucleophilicities by *N* and s_N. The electrophilicities *E* of some diazoalkanes have recently been quantified through the kinetics of their reactions with enamines and sulfonium ylides.[3] Furthermore, benzhydrylium ions of known electrophilicity *E* were used to calibrate the one-bond nucleophilic reactivity (*N*, s_N) of a series of acyclic diazo compounds (Figure 1b).[4,5]

The power of equation (1) to rationalize reported electrophile-nucleophile reactions in retrospect is well established.[3,6] In addition, equation (1) has been used as a valuable tool for the design of novel organic syntheses.[7] Recent reinvestigations on the underlying factors that influence the kinetics of 1,3-dipolar cycloadditions[3,8] triggered our interest to determine the nucleophilic reactivity (*N*, s_N) of a series of cyclic α-diazo carbonyl compounds **1** (Figure 1c), which are versatile reagents in organic synthesis.[9]

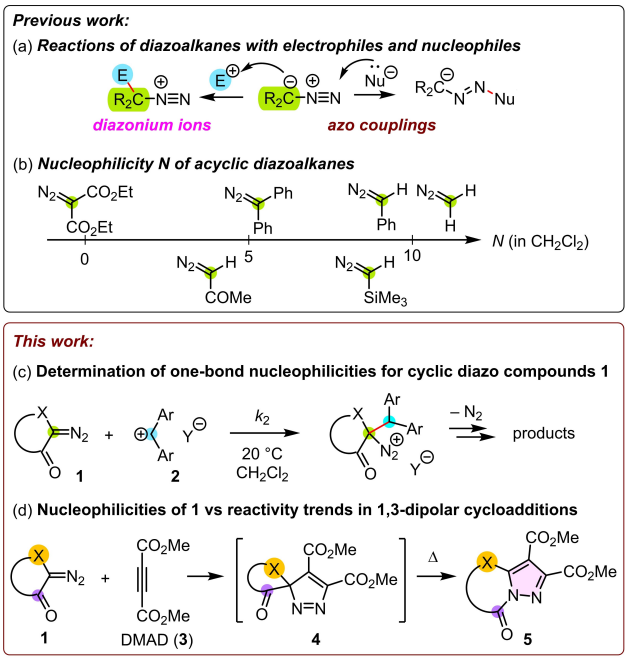

Figure 1. Reactivity of diazoalkanes and outline of the studies in this work.

Diazoalkanes are most prominent for their reactions as 1,3-dipoles in (3 + 2)-cycloadditions (Huisgen reactions) to furnish five-membered heterocycles.[1,10] In pericyclic reactions, however, concerted bond formations impede the straightforward application of equation (1) because they involve more than just one bond formation in the rate-determining step. Nevertheless, in this work, we assessed whether the experimentally assigned one-bond nucleophilicities *N* of the diazo compounds **1** also reflect reactivity trends in 1,3-dipolar cycloadditions (1,3-DCAs) of **1** with dimethyl acetylenedicarboxylate (DMAD, **3**). The 1,3-DCAs of **1** with DMAD are particularly promising because it has been shown that the initially formed (3 + 2)-cycloadducts **4** are capable of undergoing thermal acyl migration[11,12] to yield novel types of *N*-acyl pyrazoles **5** (Figure 1d).

[a] *L. Li, J.-R. Hsu, H. Zhao, Dr. A. R. Ofial*
Department Chemie,
Ludwig-Maximilians-Universität München
Butenandtstr. 5–13, 81377 München (Germany)
E-mail: ofial@lmu.de
https://www.cup.uni-muenchen.de/oc/ofial

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Results and Discussion

First, we synthesized the cyclic α-diazo carbonyl compounds **1a**–**1k** (Figure 2) by following reported protocols (see Supporting Information for details).

Next, photometric methods were applied to characterize the nucleophilic reactivity of the diazo compounds **1** by using Mayr's benzhydrylium methodology.[2c] At 20 °C colored solutions of preformed benzhydrylium tetrafluoroborates (**2a**–**c**) or tetrachlorogallates (**2d**–**h**) in dichloromethane were mixed with an excess of **1** (in CH_2Cl_2), which caused the mono-exponential decay of the benzhydryliums' absorbance, as exemplified in Figure 3a.

Fitting the absorbance decay detected at or close to the absorption maximum of **2** by the mono-exponential function, equation (2), furnished the first-order rate constants k_{obs} (s^{-1}).

$$A_t = A_0 \exp(-k_{obs}t) + C \quad (2)$$

Plotting k_{obs} of kinetic experiments determined at four different concentrations of **1** vs. [**1**] gave linear correlations

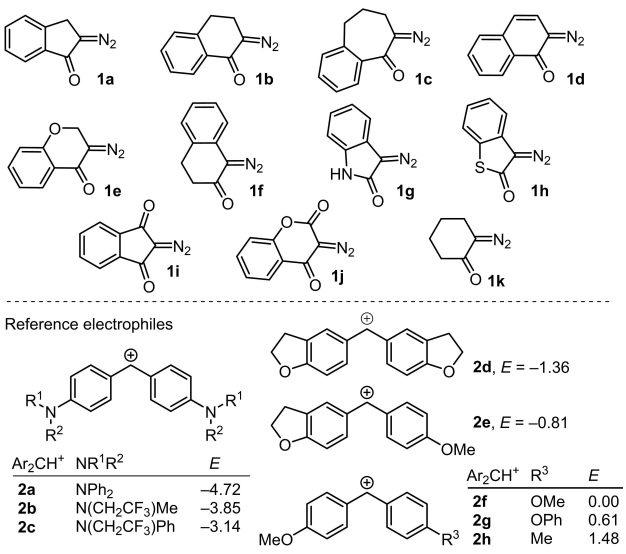

Figure 2. Investigated cyclic α-diazo carbonyl compounds **1** and structures of reference electrophiles used to determine the one-bond nucleophilicities of **1**.

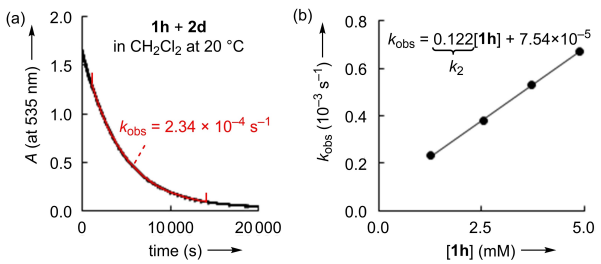

Figure 3. (a) Decay of the absorption of reference electrophile **2d** (at 535 nm) in the reaction with **1h** ([**1h**] = 1.27 mM). (b) Determination of the second-order rate constant k_2 for the reaction of **1h** with **2d**.

whose slopes correspond to the second-order rate constants k_2 ($M^{-1}s^{-1}$) of the bimolecular reactions. Figure 3b, for example, depicts the determination of k_2 for the reaction of 3-diazobenzo[*b*]thiophen-2(3*H*)-one (**1h**) with the benzhydrylium ion **2d**. Only three data points were available to derive k_2 for the reactions of **1a** with **2a** and **1g** with **2d**, respectively. All second-order rate constants k_2 determined in this work are summarized in Table 1.

Finally, the nucleophile-specific reactivity descriptors *N* (and s_N) of the diazo compounds **1** were determined according to equation (1) from the linear relationships between lg k_2 and the electrophilicity parameters *E* of the reference benzhydrylium ions **2** (Figure 4).

Table 1. Second-order rate constants k_2 for the reactions of the diazo compounds **1** with the reference electrophiles **2** (CH_2Cl_2, 20 °C).

Diazo Compounds	Electrophiles	k_2 ($M^{-1}s^{-1}$)	*N* (s_N) of **1**
1a	**2a**	3.55	5.61 (0.65)
1a	**2b**	1.59×10^{1}	
1a	**2c**	3.73×10^{1}	
1b	**2a**	8.78×10^{-2}	3.51 (0.86)
1b	**2b**	4.41×10^{-1}	
1b	**2c**	2.61	
1b	**2d**	6.68×10^{1}	
1c	**2b**	7.61×10^{-2}	2.72 (0.96)
1c	**2c**	4.15×10^{-1}	
1c	**2d**	2.31×10^{1}	
1c	**2e**	6.05×10^{1}	
1g	**2b**	2.22×10^{-1}	3.16 (1.03)
1g	**2c**	8.81×10^{-1}	
1g	**2d**	7.35×10^{1}	
1h	**2d**	1.22×10^{-1}	0.40 (0.93)
1h	**2f**	3.08	
1h	**2g**	6.27	
1h	**2h**	6.20×10^{1}	
1i	**2d**	1.05×10^{-1}	0.16 (0.86)
1i	**2f**	1.07	
1i	**2g**	4.66	
1i	**2h**	2.92×10^{1}	
1k	**2a**	9.28×10^{-2}	3.44 (0.83)
1k	**2b**	4.50×10^{-1}	
1k	**2c**	1.52	
1k	**2d**	5.75×10^{1}	

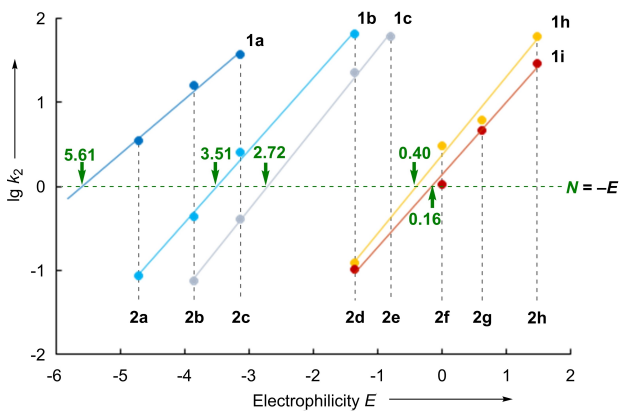

Figure 4. Determination of the nucleophilicities *N* (and s_N) of **1** from the linear relationships of lg k_2 with the electrophilicities *E* of the reference electrophiles **2** (graphs for **1g** and **1k** omitted for clarity, see Supporting Information).

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Further details of the kinetics experiments and the data evaluation to determine the N and s_N parameters of **1** are given in the Supporting Information.

Figure 5 depicts that the one-bond nucleophilicities for the investigated cyclic α-diazo carbonyl compounds **1a**–**1k** cover a reactivity range of more than five logarithmic units spanning from the most reactive 2-diazoindan-1-one (**1a**, $N = 5.61$) to the weakly nucleophilic diazoindan-1,3-dione (**1i**, $N = 0.16$). Only the previously determined reactivity of diethyl diazomalonate ($N = -0.35$)[4] falls below that of **1i**. Diazo compound **1j** is significantly less reactive than **1i**. The nucleophilicity of **1j** could not be quantified, however, because decomposition of the highly reactive benzhydrylium ions, which are needed for the kinetic studies, was faster than their reactions with **1j**.

Phenyldiazomethane ($N = 9.35$) or diazomethane ($N = 10.48$),[4,13] which lack stabilizing electron-withdrawing groups in vicinity to the diazo groups, are considerably stronger nucleophiles than the diazo compounds **1a**–**1k** investigated in this work. Interestingly, the nucleophilicity descriptors of 2-diazocyclohexanone (**1k**, $N = 3.44$, $s_N = 0.83$) are almost the same as for the 2-diazo-1-tetralone (**1b**, $N = 3.51$, $s_N = 0.86$), which may reflect an almost negligible influence of the benzoannulation on the nucleophilicity of the diazo compounds **1**. Analogously, the CH acidities of cyclohexanone ($pK_a = 26.4$ in DMSO)[14] and 1-tetralone ($pK_a = 24.7$ in DMSO)[14] indicate a similar stabilization of the corresponding enolate ions for both ketones and an insignificant effect of benzoannulation.

The susceptibilities s_N (0.83 to 1.03) of **1b**–**1k** are in a similar range as those of previously characterized non-cyclic diazo compounds (0.75 to 0.95),[4,5,13] which facilitates semiquantitative reactivity comparisons by solely considering the nucleophilicities N (in CH_2Cl_2) of the diazo compounds. Only **1a** has a significantly lower $s_N = 0.65$, which requires the use of all three reactivity parameters in equation (1) for accurate reactivity predictions.

A more general overview that includes reactivity comparisons to further C–nucleophiles is possible by using the entries in Mayr's reactivity database, which currently lists >130 C-centered nucleophiles with N values in the range $0 < N < 5$.[13]

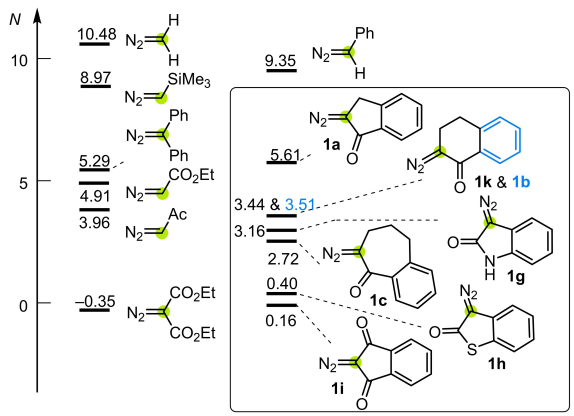


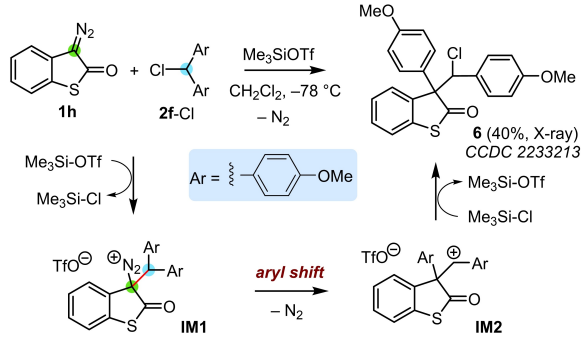
Figure 5. Nucleophilicities (N) of cyclic and acyclic diazo compounds (in dichloromethane solution).

Thus, the cyclic diazo compounds **1a–i** have one-bond nucleophilic reactivities comparable to those of terminal alkenes ($0 < N < 3$), allylsilanes, ethyl vinyl ether ($N = 3.92$), ynamides, or pyrrole ($N = 4.63$). Electrophiles that react with these nucleophiles ($0 < N < 5$) also have the potential to react at a sufficient rate with the cyclic α-diazo carbonyl compounds **1** studied in this work.

Reactions of acyclic diazo compounds with benzhydrylium ions generally give alkenes with or without rearranged carbon skeleton.[4] As shown in Scheme 1, the reaction of the cyclic diazo compound **1h** with **2f** furnished the 3,3-disubstituted benzo[*b*]thiophen-2(3*H*)-one **6**, which after chromatographic purification was isolated as a single diastereomer in 40% yield (X-ray crystal structure CCDC 2233213). The formation of **6** is rationalized by an initial carbon-carbon bond-forming attack of **1h** at **2f** (generated from **2f**-Cl and trimethylsilyl triflate) to form the diazonium triflate **IM1**. Upon dediazotation and concomitant or subsequent aryl migration the benzylic cation **IM2** is generated. Given that **IM2** cannot undergo deprotonation to an alkene, it instead abstracts a chloride ion from trimethylsilylchloride to give **6**.

Assuming analogous reactions of benzhydrylium ions with all cyclic diazo compounds **1** and given that the general synthetic chemistry of diazo compounds towards other types of C-electrophiles is well known,[1,4,8a] we have not undertaken further product studies of the kinetically investigated reactions. Instead, we turned our attention to the reactivity of **1a**–**1j** in 1,3-DCAs with DMAD (**3**).[15] Owing to the outstandingly high migration tendency of acyl groups,[11,12,16] 1,3-DCAs of DMAD (**3**) with cyclic α-diazo carbonyl compounds **1** enable one to use the van Alphen-Hüttel rearrangement to target the selective enlargement of the central ring in pyrazole-fused tricyclic compounds. Sporadic use of this ring expansion strategy has been reported for bicyclic products,[17,18] but systematic investigations to furnish tricyclic products are still scarce.[19–21]

Diazoalkane **1a**, which was characterized to be the most nucleophilic ($N = 5.61$) among the diazo compounds in this study, reacted with **3** already at 34 °C within 3.5 h to furnish **5a** in a yield of 62% (Scheme 2). Subsequent screening for the optimum reaction conditions (Supporting Information) showed that performing the reactions of **1** with **3** (2 equiv) in toluene at 75 °C was generally applicable to synthesize the tricyclic



Scheme 1. Reaction of **1h** with **2f**.

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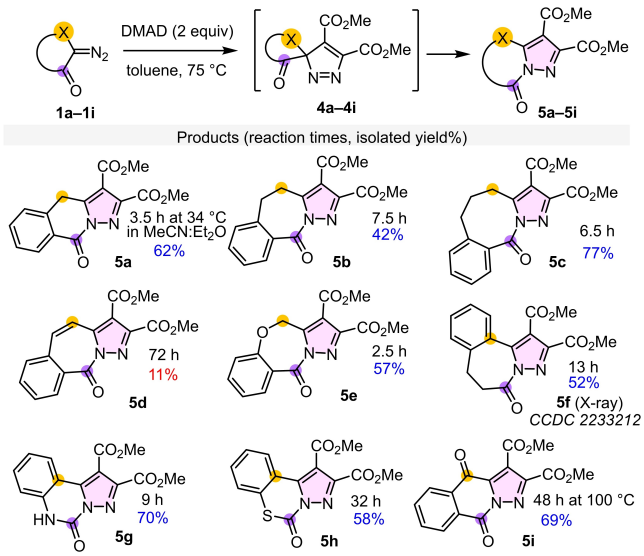

Scheme 2. Synthesis of the pyrazole-fused tricycles **5**.

products **5b**–**5i** in yields of 42 to 77% for isolated products (Scheme 2). The reaction of 2-diazonaphthalen-1(2*H*)-one (**1d**) with **3** (on 1 mmol scale) led to complete consumption of the starting materials but resulted in a dark brown reaction mixture, from which **5d** was isolated in a yield of only 11%. Still, the 10*H*-benzo[*e*]pyrazolo[1,5-*a*]azepin-10-one core of **5d**, to the best of our knowledge, resembles a so far unprecedented heterocyclic scaffold.[22] Additional decomposition products of **4d** could not be identified. All pyrazole derivatives **5a**–**5i** were fully characterized by spectroscopic methods (NMR, IR, and HR-MS). Crystals of **5f** were suitable for a single crystal X-ray structure determination (CCDC 2233212).

The initially formed (3+2)-cycloadducts **4** were not detected, which suggests that the 1,3-dipolar cycloaddition is the rate-limiting step, which is followed by a relatively fast [1,5]-sigmatropic rearrangement which shifts the acyl group from the quaternary carbon of the 3*H*-pyrazole to the adjacent nitrogen atom to yield *N*-acyl 1*H*-pyrazoles **5**.

As discussed above, equation (1) cannot be used to predict the rate constants of concerted cycloadditions because the reactivity parameters *E*, *N*, and s_N in equation (1) have been calibrated to describe the rate of reactions in which only one new σ-bond is formed. Breugst and colleagues had reported, however, that the quantum-chemically calculated transition state geometry for the reaction of diazomethane with DMAD (**3**) is characterized by a short C–C distance (2.12 Å) and a longer C–N distance (2.67 Å),[23] which indicate significantly asynchronous bond formations in the course of the concerted 1,3-dipolar cycloadditions of diazo compounds with dialkyl acetylenedicarboxylates.

It is interesting to note, therefore, that the dipolarophile **3** reacted with diazo compounds **1a**–**c**, **g** of $N>2$ in less than 10 h of reaction time. The less nucleophilic **1h** and **1i** needed extended reaction times and/or higher temperatures to become effective, and the even weaker nucleophile **1j** entirely failed to deliver a product in the reaction with **3** (after 50 h at 75 °C).

This reactivity trend is in accord with the more advanced carbon-carbon bond formation in the transition state of the concerted 1,3-DCAs of **1** with DMAD (**3**). Thus, the reactions in Scheme 2 give another example for the observation that relative nucleophilicities, as described by the Mayr *N* parameters, towards a common electrophilic reaction partner may also hold for more complex, concerted reactions.[24,25]

Conclusion

The nucleophilicity parameters *N* (and s_N) determined in this work facilitate the prediction of novel reactions of the cyclic α-diazo carbonyl compounds **1** with various types of electrophiles. Similar reactivity trends for **1** were also observed in reactions with DMAD, used as an electrophilic dipolarophile. Reactions of **1** with DMAD gave pyrazoles, which are structural motifs in pharmaceuticals. In particular, *N*-acyl pyrazoles were shown to be selective inhibitors of various hydrolases.[26–29] Thus, the investigated (3+2)-cycloaddition/[1,5]-sigmatropic rearrangement cascade may in the future be further exploited to generate bioactive, polycyclic pyrazole derivatives.

Experimental Section

Analytics: ^{1}H and $^{13}C\{^1H\}$ NMR spectra were recorded in $CDCl_3$ (δ_H 7.26, δ_C 77.16 ppm) or CD_3CN (δ_H 1.94, δ_C 1.32 ppm) on 400 or 800 MHz NMR spectrometers.[30] The following abbreviations were used for the designation of chemical shift multiplicities: br = broad, s = singlet, d = doublet, t = triplet, quint = quintet, m = multiplet. NMR signals were assigned by additional 2D NMR experiments (COSY, HSQC, HMBC and NOESY), which were also used to derive the reported multiplicities (C, CH, CH_2, or CH_3) of $^{13}C\{^1H\}$ resonances. IR spectra were recorded on a FTIR Spectrometer SPECTRUM BX II with an ATR probe (Perkin Elmer). HRMS were recorded on a Thermo Finnigan LTQ FT Ultra (ESI) or a Finnigan MAT 95Q (EI) mass spectrometer. Melting points were determined on a Büchi B540 device and were not corrected. All X-ray intensity data were measured on a Bruker D8 Venture TXS system equipped with a multilayer mirror monochromator and a Mo Kα rotating anode X-ray tube (λ = 0.71073 Å).

Chemicals: The cyclic α-diazo carbonyl compounds **1** were synthesized according to previously reported procedures and characterized by their NMR spectra (Supporting Information). 2-Diazo-1-benzosuberone (**1c**) was fully characterized (NMR and IR spectra, HRMS) as spectroscopic data for this diazo compound had not been reported previously. Benzhydrylium tetrafluoroborates **2a**–**2c** were prepared as described in Ref. [31] The diarylchloromethanes (**2d**–**2h**-Cl) were synthesized as reported in Ref. [32] Dimethyl acetylenedicarboxylate (99%) was purchased from Sigma-Aldrich and used as received.

Kinetics: Kinetic investigations were performed in dry dichloromethane at 20 °C by using a J&M TIDAS diode array spectrometer system connected to a Hellma all-quartz immersion probe. The temperature of the reaction mixtures was kept constant at 20.0 ± 0.1 °C by using a circulating bath thermostat. All UV-vis kinetic experiments were performed with a high excess (>7 equiv) of the diazo compounds **1** over the benzhydrylium ion **2** to achieve

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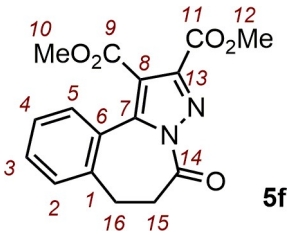
pseudo first-order conditions. Benzhydrylium ions **2d–h** (counter-ion: $GaCl_4^-$) were freshly prepared for each kinetic measurement by adding 2.5 to 3.5 equivalents of $GaCl_3$ solution in dry dichloromethane to a solution of a certain diarylchloromethane (**2**-Cl) in dry dichloromethane. Rate constants k_{obs} (s^{-1}) were obtained by fitting the single exponential decay function, equation (2), to the observed time-dependent absorbance of the benzhydrylium ions **2**. The second-order rate constants k_2 ($M^{-1}s^{-1}$) were derived from the slopes of the linear correlations of k_{obs} (s^{-1}) with concentrations of **1**. Details of the individual kinetic measurements are given in the Supporting Information.

Exemplary Procedure for the Synthesis of 5: 1-Diazo-2-tetralone **1f** (104 mg, 0.604 mmol) was mixed with a solution of DMAD **3** (170 mg, 1.20 mmol) in toluene (1 mL). The reaction mixture was stirred at 75 °C for 13 h (TLC control). After storing the reaction mixture at +6 °C overnight, formation of precipitates was observed. The solid material was isolated by filtration and washed with cold Et_2O (3×1 mL) to afford dimethyl 5-oxo-6,7-dihydro-5*H*-benzo[*c*]-pyrazolo[1,5-*a*]azepine-1,2-dicarboxylate (**5f**) (98 mg, 52%) as a white solid; m.p. 168–169 °C; R_f = 0.21 (silica gel, *n*-pentane : EtOAc = 1 : 1 v/v).

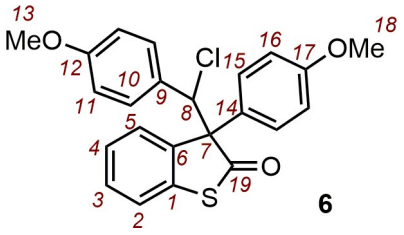


5f

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.02–3.05 (m, 2 H, 16-H), 3.20–3.23 (m, 2 H, 15-H), 3.86 (s, 3 H, 10-H), 3.98 (s, 3 H, 12-H), 7.32 (dd, *J* = 7.7, 1.6 Hz, 1 H, 2-H), 7.37 (td, *J* = 7.6, 1.5 Hz, 1 H, 4-H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1 H, 3-H), 7.61 (dd, *J* = 7.6, 1.5 Hz, 1 H, 5-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.3 (CH_2, C-16), 40.2 (CH_2, C-15), 52.95 (CH_3, C-12), 53.04 (CH_3, C-10), 117.2 (C, C-8), 125.6 (C, C-6), 127.8 (CH, C-4), 128.6 (CH, C-2), 130.8 (CH, C-5), 131.4 (CH, C-3), 139.6 (C, C-1), 144.1 (C, C-7), 145.3 (C, C-13), 161.5 (C, C-11), 163.7 (C, C-9), 169.0 (C, C-14). HRMS (ESI^+): *m/z* calcd. for $C_{16}H_{15}N_2O_5^+$ $[M+H^+]$: 315.0975; found: 315.0977. IR (neat, ATR): 2965, 1743, 1727, 1585, 1548, 1479, 1461, 1436, 1422, 1329, 1294, 1278, 1233, 1202, 1162, 1114, 1098, 1069, 982, 954, 900, 848, 810, 794, 777, 758, 708 cm^{-1}.

Procedures and analytical data for all other isolated products **5** are given in the Supporting Information.

3-(Chloro(4-methoxyphenyl)methyl)-3-(4-methoxyphenyl)benzo-[*b*]-thiophen-2(3*H*)-one (**6**) was obtained by dissolving di(*p*-anisyl)-chloromethane **2f**-Cl (248 mg, 0.94 mmol) and trimethylsilyl triflate (267 mg, 1.20 mmol) in anhydrous CH_2Cl_2 (12 mL) at −78 °C. Subsequently, a solution of **1h** (357 mg, 2.03 mmol) in CH_2Cl_2 (5 mL) was added. Stirring at −78 °C continued for 5.5 h. Then, conc. ammonia (20 mL) was added. After extraction with CH_2Cl_2 (2× 20 mL), the combined organic fractions were dried ($MgSO_4$), and the volatiles were removed under vacuum. The crude material was purified by column chromatography (silica gel, eluent: n-pentane/diethyl ether = 8 : 1). Volatiles of the main fraction were removed under vacuum. Crystallization of the residue (from CH_2Cl_2/hexane) yielded diastereomerically pure **6** (158 mg, yield 40%) as a light-pink solid; m.p. 155.3 °C; R_f = 0.33 (silica gel, *n*-pentane : Et_2O = 8 : 1, v/v).



6

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, 13-H), 3.81 (s, 3 H, 18-H), 6.01 (s, 1 H, 8-H), 6.58–6.62 (m, 2 H, 11-H), 6.84–6.89 (m, 2 H, 10-H), 6.89–6.92 (m, 2 H, 16-H), 7.22–7.24 (m, 1 H, 2-H), 7.27–7.30 (m, 2 H, 15-H), 7.37–7.44 (m, 2 H, 3-H and 4-H), 7.92–7.94 (m, 1 H, 5-H). ^{13}C NMR (201 MHz, $CDCl_3$): δ = 55.3 (CH_3, C-13), 55.4 (CH_3, C-18), 66.2 (CH, C-8), 72.3 (C, C-7), 113.2 (CH, C-11), 114.2 (CH, C-16), 122.9 (CH, C-2), 126.1 (CH, C-4), 127.9 (C, C-9), 129.3 (CH, C-5), 129.4 (CH, C-15), 129.6 (CH, C-3), 129.8 (C, C-14), 130.3 (CH, C-10), 136.3 (C, C-6), 136.8 (C, C-1), 159.5 (C, C-17), 159.8 (C, C-12), 205.0 (C, C-19). HRMS (EI): *m/z* calcd. for $C_{23}H_{19}ClO_3S^{+\bullet}$ $[M^{+\bullet}]$: 410.0738; found: 410.0745. IR (neat, ATR): 3000, 2957, 2930, 2834, 1698, 1609, 1514, 1460, 1446, 1286, 1257, 1241, 1183, 1081, 1032, 1004, 872, 839, 820, 793, 766, 739, 697 cm^{-1}.

Deposition Numbers CCDC 2233212 and CCDC 2233213

Deposition Numbers 2233212 (for **5f**), 2233213 (for **6**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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