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Arylhydrazones of α-keto esters *via* methanolysis of dichlorodiazabutadienes: synthesis and structural study

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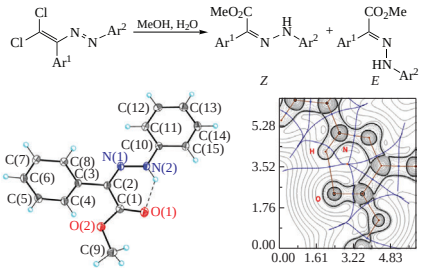
Novel approach to methyl 2-aryl-2-(arylhydrazono)acetates *via* methanolysis of dichlorodiazabutadienes was developed. Hydrogen bonding in methyl *Z*-2-phenyl-2-(phenylhydrazono)acetate was explored by DFT calculations and topological analysis of the electron density distribution within the framework of Bader's theory (QTAIM method).



Keywords: keto esters, hydrazones, hydrogen bonding, DFT, QTAIM, calculations, methanolysis.

Hydrazone functionality is an ubiquitous element in various fields including synthetic, medicinal, coordination chemistry and many others.[1–10] *N*-Arylhydrazones are important precursors in the Fischer synthesis of indoles, which are present in many pharmacologically active compounds.[11] *N*-Arylhydrazones are usually prepared *via* the condensation of carbonyl compounds with *N*-arylhydrazines,[8] although several alternative routes are also available, *i.e.* reaction between arene diazonium salts and β-keto esters,[12] or the Buchwald cross coupling of non-substituted hydrazones with aryl halides.[13] Recently, we described novel dichlorodiazabutadienes which can be accessed in a straightforward way *via* the copper-catalyzed reaction between CCl_4 and arylhydrazones.[14] These dichlorodiazabutadienes are the promising building blocks in organic synthesis to prepare various attractive compounds.[14–23] Here, we describe the synthesis of methyl 2-aryl-2-(arylhydrazono)acetates *via* the alcoholysis of 4,4-dichloro-1,2-diazabuta-1,3-dienes.

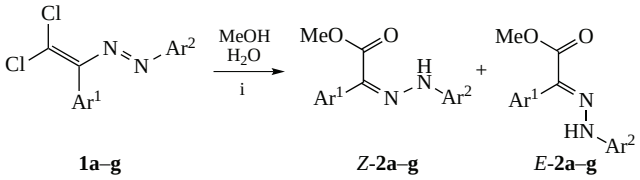
When the starting dichlorodiazadienes **1a–g** were kept in aqueous methanol for 2 h at room temperature, the reaction mixture gradually changed the color from orange-red to yellow. Subsequent work up allowed the corresponding α-keto ester hydrazones **2a–g** to be isolated in up to 80% yields (Scheme 1, for details, see Online Supplementary Materials). The products **2a–g** were formed as mixtures of *E*- and *Z*-isomers in approximately 1 : 1 ratio. The isomers could be readily separated by column chromatography. The structures of *Z*-**2a–g** and *E*-**2a–g** were confirmed by the ^{1}H and ^{13}C NMR spectroscopy, while X-ray diffraction analysis was performed for *Z*-**2a** and *E*-**2a** (Figure 1 and Table S1 of Online Supplementary Materials).[†] Overall, metrical parameters for *Z*-**2a** and *E*-**2a** are close to those found for earlier described β-keto ester hydrazones[24,25] and other similar hydrazones and azo compounds.[16,18,20,23,26–35]

Interestingly, compound *Z*-**2a** featured an intramolecular hydrogen bonding. In order to confirm or deny the existence of

[†] *Crystal data for Z-***2a**. A yellow prismatic crystal [$C_{15}H_{14}N_2O_2$ (M_r = 254.28)] is triclinic, space group $P\bar{1}$, at T = 100 K: a = 5.6248(2), b = 11.0265(4) and c = 11.3986(4) Å, α = 116.458(1)°, β = 92.796(1)°, γ = 94.705(1)°, V = 627.89(4) Å^3, Z = 2, d_{calc} = 1.345 g cm^{-3}, $F(000)$ = 268, μ = 0.091 mm^{-1}. 11413 reflections (4564 independent reflections, R_{int} = 0.031) were measured and used in the refinement. The refinement converged to R_1 = 0.046 for 3557 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.125 for all independent reflections, S = 1.023.

*Crystal data for E-***2a**. A colorless prismatic crystal [$C_{15}H_{14}N_2O_2$ (M_r = 254.28)] is orthorhombic, space group *Pbca*, at T = 100 K: a = 14.5296(7), b = 9.0450(4) and c = 19.6205(10) Å, V = 2578.5(2) Å^3, Z = 8, d_{calc} = 1.310 g cm^{-3}, $F(000)$ = 1072, μ = 0.089 mm^{-1}. 54957 reflections (3071 independent reflections, R_{int} = 0.100) were measured and used in the refinement. The refinement converged to R_1 = 0.059 for 1614 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.151 for all independent reflections, S = 1.007.

The measurements were performed on a Bruker D8 QUEST diffractometer using a PHOTON III CCD detector, λ(MoK$_\alpha$)-radiation, graphite monochromator, φ and ω scan mode, and corrected for absorption using the SADABS program.[45] The data were indexed and integrated using the SAINT program.[46] For details, see Online Supplementary Materials. The structures were determined by direct methods[47] and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The



1a–g *Z*-**2a–g** *E*-**2a–g**

a $Ar^1 = Ar^2 = Ph$
b $Ar^1 = Ph$, $Ar^2 = 4\text{-}MeC_6H_4$
c $Ar^1 = Ph$, $Ar^2 = 3,5\text{-}Me_2C_6H_3$
d $Ar^1 = 4\text{-}ClC_6H_4$, $Ar^2 = 4\text{-}MeC_6H_4$
e $Ar^1 = 4\text{-}BrC_6H_4$, $Ar^2 = 3,5\text{-}Me_2C_6H_3$
f $Ar^1 = 3\text{-}O_2NC_6H_4$, $Ar^2 = 4\text{-}MeC_6H_4$
g $Ar^1 = 3\text{-}O_2NC_6H_4$, $Ar^2 = Ph$

Scheme 1 *Reagents and conditions*: i, room temperature, 2 h.

intramolecular hydrogen bonding N–H···O in *Z*-**2a** and theoretically quantify energy of these non-covalent interactions, we carried out DFT calculations at the B97-3c[36] level of theory. Moreover, topological analysis of the electron density distribution within the framework of Bader's theory (QTAIM analysis)[37] was performed for the optimized equilibrium model structure *Z*-**2a** (see Online Supplementary Materials, Table S1). Results of QTAIM analysis are summarized in Table 1, the contour line diagram of the Laplacian of electron density distribution $\nabla^2\rho(\mathbf{r})$, bond paths, and selected zero-flux surfaces for intramolecular hydrogen bonding N–H···O in the optimized equilibrium model structure *Z*-**2a** are shown in Figure 1. For the non-covalent interactions analysis as scatter graph of reduced density gradient (RDG) *vs*. real space function sign(λ_2)ρ, namely the product of sign of λ_2 (second largest eigenvalue of Hessian matrix of electron density) and ρ (electron density) (NCI plot)[38] for

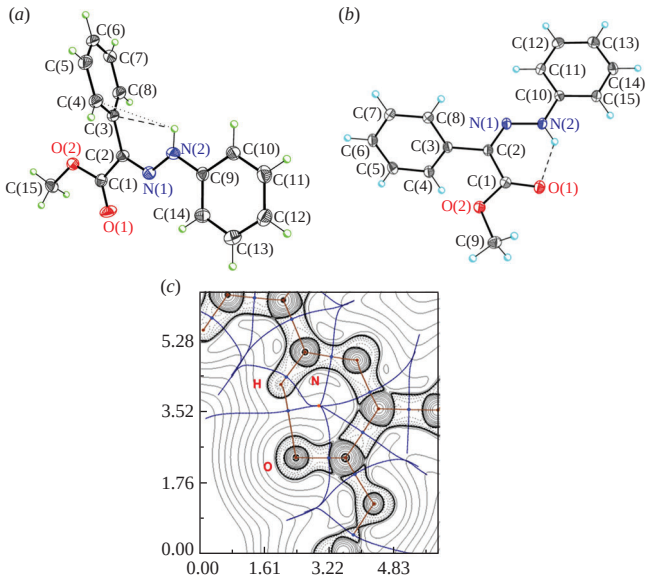


Figure 1 Molecular stuructures of isomers (*a*) *E*-**2a**, (*b*) *Z*-**2a** and (*c*) contour line diagram of the Laplacian of electron density distribution $\nabla^2\rho(\mathbf{r})$, bond paths, and selected zero-flux surfaces for intramolecular hydrogen bonding N–H···O in the optimized equilibrium model structure *Z*-**2a**. Bond critical points (3, –1) are shown in blue, nuclear critical points (3, –3) – in pale brown, ring critical points – in orange, bond paths are shown as pale brown lines, length units are given in Å.

hydrogen atoms of the amino groups were objectively localized in the difference-Fourier map and refined isotropically. The other hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [$U_{iso}(H) = 1.5U_{eq}(C)$ for the methyl groups and $1.2U_{eq}(C)$ for the other groups]. The calculations were carried out using the SHELXTL program.[48]

CCDC 2084572 (*Z*-**2a**) and 2084573 (*E*-**2a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Table 1 Calculated parameters at the bond critical point (3, –1) for intramolecular hydrogen bonding N–H···O in the optimized equilibrium model structure *Z*-**2a** and estimated strength for these non-covalent interactions E_{int} (kcal mol^{-1}).

Length of H···O contact	$\rho(\mathbf{r})$	$\nabla^2\rho(\mathbf{r})$	λ_2	H_b	$V(\mathbf{r})$	$G(\mathbf{r})$	$E_{int} = -V(\mathbf{r})/2$[39]
1.832 Å	0.037	0.138	–0.037	–0.001	–0.037	0.036	11.6

optimized equilibrium model structure *Z*-**2a** and visualization of intramolecular hydrogen bonding N–H···O in 3D using NCI analysis technique, see Figure S1.

The QTAIM analysis demonstrates the presence of appropriate bond critical point (3, –1) for intramolecular hydrogen bonding N–H···O in the optimized equilibrium model structure *Z*-**2a** (Table 1). The low magnitude of the electron density, positive value of the Laplacian of electron density, and very close to zero energy density in this bond critical point (3, –1) and estimated energy for appropriate short contact (11.6 kcal mol^{-1}) (see Table 1) are typical of moderate strength hydrogen bonding following the classification of Jeffrey (weak: <4 kcal mol^{-1}, moderate: 15–4 kcal mol^{-1}, strong: 40–15 kcal mol^{-1}).[40–42] The balance between the Lagrangian kinetic energy $G(\mathbf{r})$ and potential energy density $V(\mathbf{r})$ at the bond critical point (3, –1) corresponding to intramolecular hydrogen bonding N–H···O in the optimized equilibrium model structure *Z*-**2a** reveals the existence of some small covalent contribution in this contact.[43] The Laplacian of electron density is typically decomposed into the sum of contributions along the three principal axes of maximal variation, giving the three eigenvalues of the Hessian matrix (λ_1, λ_2 and λ_3), and the sign of λ_2 can be utilized to distinguish bonding (attractive, $\lambda_2 < 0$) interactions from nonbonding ones (repulsive, $\lambda_2 > 0$).[38,44] Thus, intramolecular hydrogen bonding N–H···O in the optimized equilibrium model structure *Z*-**2a** is attractive (see Table 1).

In summary, the synthesis of α-keto ester hydrazones was elaborated *via* the methanolysis of dichlorodiazabutadienes. Structural study and full characterization were performed for these products. Hydrogen bonding in *Z*-**2a** was examined by DFT calculations and topological analysis of the electron density distribution within the framework of Bader's theory (QTAIM method).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.09.028.

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