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Isocyanide Cyclization Reactions: 4-Methylene-4*H*-benzo[*d*][1,3]oxazine, 3-Benzyl-4-methylene-3,4-dihydroquinazolines and 3-(4-Benzyl)-3*H*-quinazolin-4-ones – Experiment and Theory

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2-Isocyanoacetophenone (**3a**) was found to be an easily accessible starting material for the unexpected formation of various heterocyclic systems. Thus, a hitherto unknown rather unstable 4-methylene-4*H*-benzoxazine derivative **4**, which could be characterized by NMR spectroscopy, was formed in situ by the reaction of **3a** in the presence of weak acids. In the presence of benzylamines, a new class of 3,4-dihydroquinazoline derivatives **6** and their oxidation products, quinazolin-4-ones **9**, were obtained. The starting materials and products were completely characterized by spectroscopic and X-ray analysis. The scope and limitations of these cyclization reactions were investigated under various reaction conditions. High-level quantum chemical calculations were carried out to elucidate the mechanisms leading to scaffolds **4** and **6**. The calculations suggest that the formation of **4** and **6** involves the generation of an unusual six-membered *N*-heterocyclic carbene or its *C*-protonated form as a reaction intermediate, followed by tautomerisation. This mechanism might also be applicable to other isocyanide cyclization reactions.

Introduction

Due to their unique ability to react both as an electrophile and a nucleophile at carbon, isocyanides are chemical building blocks with a wide range of applications, especially in heterocyclic chemistry.[1,2] In the course of our studies on the cyclization reactions of aza-polyenyl anions, which led to several new routes for the synthesis of 5-, 6-, 7-, and even 14-membered heterocyclic ring systems,[3] we became interested in benzyl imines **7**, derived from 2-isocyanoacetophenone **3a** as the carbonyl component. We anticipated that these imines (i.e., **7**) could be used as precursors to the corresponding anions, which could undergo ring-closure reactions to give heterocyclic compounds by a new anionic reaction pathway. Compound **3a** is known to be rather unstable, and its reactivity has not yet been studied in detail. For example, its reactions with amines are, to the best of our knowledge, unknown.

In this paper, we describe unexpected reactions leading to various quinazoline derivatives **6** and their oxidation products, quinazolin-4-ones **9**, with unique substitution patterns. They were obtained during the attempted conversion of ketone **3a** with benzylic amines into the corresponding imines (i.e., **7**). In the absence of amines, under slightly acidic conditions, **3a** unexpectedly formed benzoxazine **4**, which explains the instability of this compound, and suggests new synthetic applications of similar isocyanides.[4,5]

These experimental studies are augmented by high-level quantum chemical studies into the possible mechanism of these reactions. These quantum chemical studies focus on intramolecular nucleophilic additions of oxygen and nitrogen nucleophiles to the carbon atoms of the isocyanides, possibly after *C*-protonation under the reaction conditions. We suggest the formation of unusual six-membered *N*-heterocyclic carbene intermediates, or – which is more likely – their protonated forms.

Quinazoline-4-ones[6] and the less common 3,4-dihydroquinazolines[7] are of interest because of their manifold medicinal and pharmacological applications. Various derivatives of quinazolin-4-ones have previously been synthesized by other routes.[8]

Results and Discussion

Synthesis and Properties of Isocyanide 3

The precursors for the reactions under study, 2-isocyanophenyl ketones **3a**–**c**, were synthesized in two steps by modification of reported procedures starting from the respective

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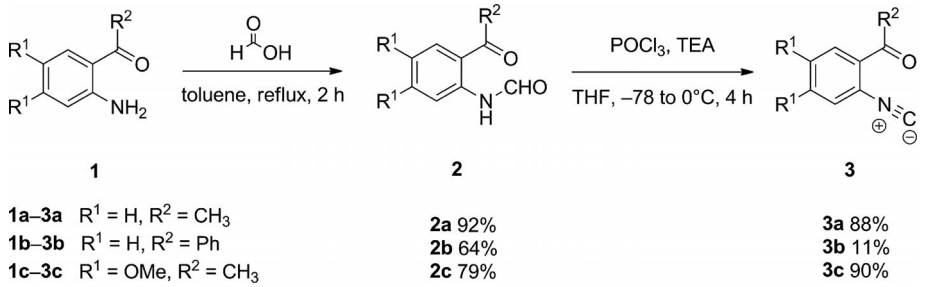


Scheme 1. Synthesis of 2-isocyanophenyl ketones **3**.

primary amines (i.e., **1a**–**c**).[9] The first step, a formylation reaction using formic acid, gave formamides **2a**–**c** (Scheme 1).

Additionally to the reported experimental data for **2a** and **2c**,[10] we were able to characterize the structures of **2a** and **2c** by X-ray diffraction (Figure 1).[11] The molecular structures of **2a** and **2c** are completely planar as a result of intramolecular hydrogen bonding (N1/N11–H···O2/O22, 1.939 Å for **2a** and 1.964 Å for **2c**). Characteristic bond lenghts for **2a** and **2c** are as follows: 1.225(3) and 1.2297(17) Å for C=O (ketone), 1.343(3) and 1.348(2) Å for N–C (formamide), and 1.221(3) and 1.213(2) Å for C–O (formamide). The X-ray structures indicate that the carbonyl and formamide functionalities of **2** are in close proximity, and this is also expected to be the case for the corresponding isocyanides (i.e., **3**), setting them up for intramolecular reactions.

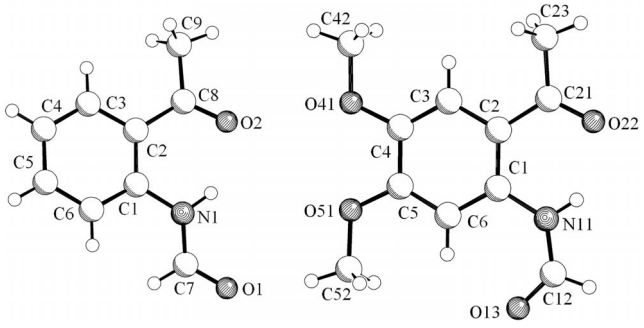
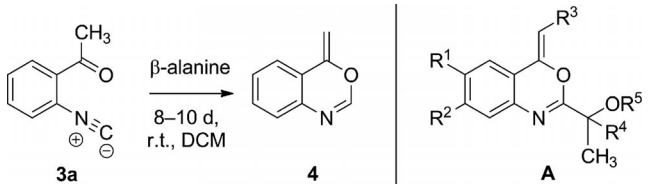


Figure 1. Molecular structures of compounds **2a** and **2c** (Schakal plot).[12]

In the second step, compounds **2** were dehydrated using phosphorus oxychloride to give isocyanides **3**. Compounds **3a** and **3c** were obtained in high yield, whereas the reaction sequence starting from 2-aminobenzophenone (**1b**) gave only a small amount of the target compound (i.e., **3b**). Compounds **3** were oils that solidified below ca. –30 °C. We were not able to obtain crystals suitable for X-ray diffraction.

Compound **3a** was reasonably stable at 0 °C, but it reacted within a few days after the addition of even weakly acidic compounds such as β-alanine to form black residues. Intermediate ^{1}H and ^{13}C NMR spectra taken of a dilute toluene solution of **3a** with a small portion of β-alanine indicated the predominant formation of 4-methylene-4*H*-benzo[*d*][1,3]oxazine (**4**; Scheme 2 and Supporting Information), which reached a maximum concentration in our experiments after about 8–10 d of reaction time. All attempts to isolate the pure compound failed, but the NMR spectra unambiguously confirmed the formation of **4**. For our investigation of the reaction mechanism (see below), we tested several solvents and reaction conditions. Dichloromethane turned out to be the best solvent. More strongly acidic conditions ($POCl_3$ or HCl) led, as expected, to decomposition, mostly into formamide **2** and black residues. Molecular sieves resulted in a slower conversion than that seen with β-alanine. Triethylamine gave no reaction at all.



Scheme 2. Synthesis of 4-methylene-4*H*-benzo[*d*][1,3]oxazine (**4**) from isocyanide **3a** (left); compounds **A** as obtained by Kobayashi et al.[13] (right).

Compound **4** is closely related to a compound reported by Kobayashi et al.,[13] who identified 2-substituted 4-alkylidene-4*H*-benzo[*d*][1,3]oxazines **A** after treatment of compounds related to **3** with vinyl ethers under mildly acidic conditions. The reaction reported here represents the basic type of cyclization reaction of less stable isocyanides such as **3**, and as such, represents the "missing link" to other isocyanide cyclizations as reported by Kobayashi[2] and other groups.[4] Substituted derivatives of compounds **4** have been prepared by Saito et al. by Palladium-catalysed cyclization of *N*-acyl-*o*-alkynylanilines.[14]

Reactions of 3 with Amines: Synthesis of Dihydroquinazolines 6 and Quinazoline-4-ones 9

Compounds **3a**–**c** were treated with various primary amines in the presence of molecular sieves.[15] Our initial aim was the preparation of imines **7**. However, the use of alkylamines such as methylamine, neopentylamine, or *tert*-butylamine in the presence of molecular sieves led only to inseparable mixtures. Benzylamines **5a**–**e** were investigated next. To our surprise, the reaction of isocyanide **3a** with **5a**–**e** did not result in the formation of the expected condensation products (i.e., **7**; Scheme 3, Table 1). Instead, from **3a**,

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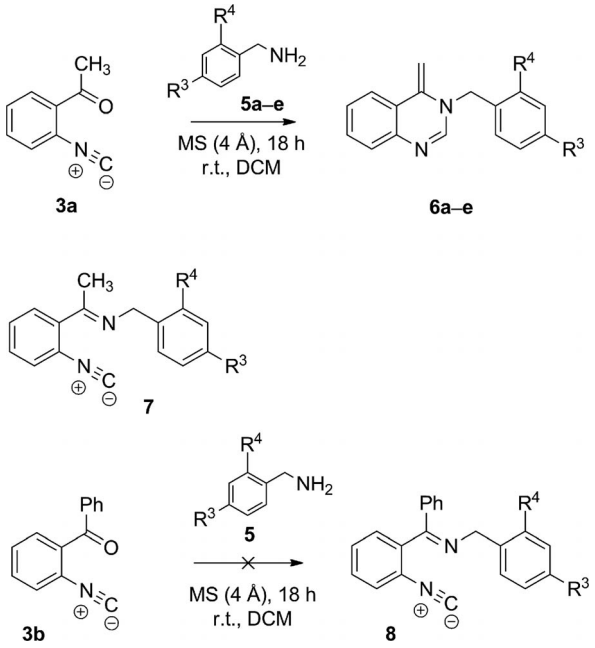
4-methylene-3,4-dihydro-quinazoline products of type **6** were obtained after crystallization under argon in moderate to good yields. We assume that the initially targeted imines (i.e., **7**) are involved as key intermediates in these reactions (see mechanistic discussion below). The reaction of dimethoxy-substituted compound **3c** with benzylamines also gave the corresponding 3,4-dihydroquinazolines, which could be identified in the crude mixtures by NMR spectroscopy and mass spectrometry. Attempts to purify these products by recrystallization failed. Column chromatography on silica or aluminium oxide resulted in decomposition, mostly into the corresponding formamide (i.e., **2c**). From the type of products obtained (i.e., **6**), it is clear that the scope of this ring-forming reaction is limited to aryl alkyl ketones. With the rather unreactive diaryl ketone **3b**, no reaction with amines to give imines was observed, even when other "smaller" amines (methylamine), harsher conditions (Brønsted or Lewis acid catalysis), and higher temperatures were used to promote the condensation reaction.



Scheme 3. Formation of **6a**–**e** by reaction of compounds **3a** with benzylamines **5** (top). Compound **7** (middle). Compound **3b** does not react with amines **5** (bottom). For the substitution patterns, see Table 1.

Table 1. Substitution patterns of compounds **5** and **6**, and isolated yields of **6**.

	R^3	R^4	Isolated yield of **6** [%]
5a, **6a**	H	H	75
5b, **6b**	CH_3	H	77
5c, **6c**	Cl	H	31
5d, **6d**	OCH_3	H	31
5e, **6e**	OCH_3	OCH_3	24

Next, we focussed our attention on optimizing the conditions of the reaction of **3a** with benzylamines to form products **6**. The best results were obtained in dichloromethane with molecular sieves. Catalytic amounts of acid (*p*-toluenesulfonic or camphorsulfonic acids) also facilitated the formation of compounds **6**, whereas bases inhibited it. An experiment using triethylamine as additional base resulted in no reaction.

Crystals suitable for X-ray diffraction analysis were grown for **6a** and **6d**. The results confirmed the structures and gave us insight into the conformational properties of these molecules (Figure 2).[11]

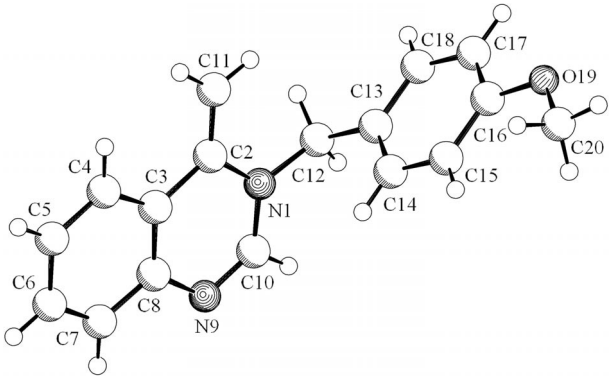
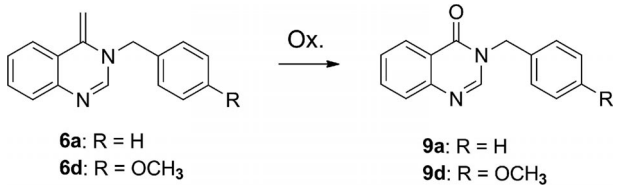


Figure 2. Molecular structure of compound **6d** (Schakal plot).[12]

The 4-methylene-3,4-dihydroquinazoline framework of **6d** is planar. The length of the imine bond N9–C10 is 1.281(3) Å, while the bond length C2–C11 is 1.325(3) Å. Furthermore, the NMR spectra of **6** show some interesting features. The signal of the proton at C10 is shifted remarkably upfield (δ = 6.96 ppm for **6a**) compared to what is usual for imines.[16] The protons of the alkene functionality resonate at δ = 3.66 (d) and 4.49 (m) ppm.

Oxidation of 6 to 9

Compounds **6a**–**e** were found to be quite sensitive towards oxidation. Thus, during column chromatography, compounds **6a**,**d** were transformed into **9a**,**d** (Scheme 4), albeit in low yield. The structures of the oxidized products were determined by 1D and 2D NMR spectroscopy and mass spectrometry, and for **9d**, the data were consistent with data reported in the literature.[17] A related type of oxidation was reported by Kim et al.[18]



Scheme 4. Oxidation of **6a**,**d** to give compounds **9a**,**d**.

To investigate this oxidation reaction in more detail, compounds **6a**,**d** were stirred in a flask exposed to air for about 7 d. We observed a conversion into the respective quinazolin-4-ones (i.e., **9a**,**d**) with a yield of about 30% (determined by NMR spectroscopy). Figure 3 shows the con-

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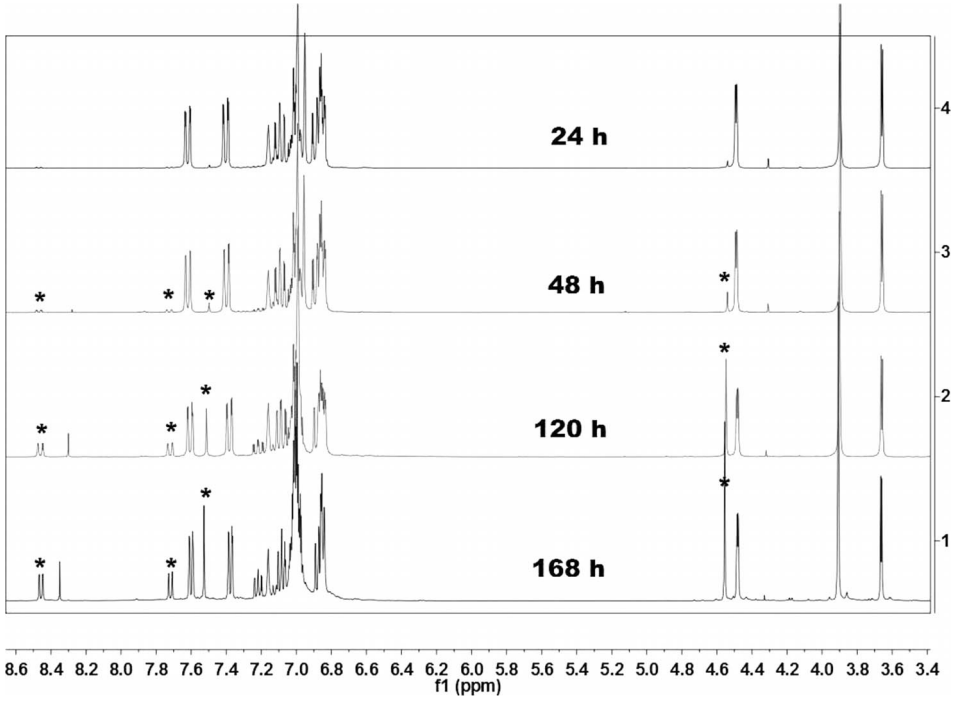

Figure 3. Reaction of **6a** to form **9a** in an NMR tube. Spectra were recorded after 24 h, 48 h, 120 h, and 168 h (solvent C_6D_6).

version of **6a** into **9a**, as monitored by ^{1}H NMR spectroscopy. While the peaks of compound **6a** decreased the signals for **9a** (marked with a *) are increasing with time.

The oxidized compounds were recrystallized from ethyl acetate. Compound **9a** was isolated in 25% yield, and **9d** in 20% yield. It was also possible to obtain **9d** by column chromatography (SiO_2, pentane/ethyl acetate). In this case, **9d** was obtained in 10% yield. For the ^{1}H and ^{13}C NMR spectra of pure compounds **9a**,**d** in CD_2Cl_2, see Supporting Information. Attempts to increase the conversion or yield by filtration through SiO_2 or by using DDQ as an oxidant were not successful. Further studies to improve this oxidation reaction are ongoing.

Reaction Mechanism

The unexpected formation of six-membered N,O and N,N heterocyclic species starting from compounds **3** prompted us to investigate the possible reaction mechanisms by quantum chemical calculations at the SCS-MP2/6-311+G(d,p)//B3LYP/6-31+G(d),[19,20] level of theory.

At first, we studied the cyclization reaction of **3a** to give **4** computationally (Scheme 5). The cyclization of the neutral compound can be excluded, as the necessary intermediate carbene (i.e., **10**) does not correspond to a local minimum on the energy hypersurface. However, the proton-catalysed pathway (protonation at the isocyanide carbon atom to give **12**, rather then at oxygen to give **11**, lower line) is quite exothermic (–16.8 kcal mol^{-1}), and leads to **13** with a very small activation barrier (2.5 kcal mol^{-1}). Loss of a proton leads to the final product (i.e., **4**). Based on chemical intuition, it seems likely that compound **4**, an enol ether, would be rather sensitive to an acidic environment. Therefore, the results obtained from this series of calculations support the experimental data for the formation of this interesting enol ether **4**, which, as an intermediate or if isolated, might be a useful building block in organic synthesis.

Secondly, we investigated the formation of 3-benzyl-4-methylene-3,4-dihydroquinazoline (**6a**; Scheme 6). Here, we assume that the condensation reaction of **3a** with benzylamine **5a** first leads to intermediate **7**. Taking **7** as the starting point, we considered two pathways. The first one, involving neutral imine **7**, is based on an interaction between the lone pair of the imine nitrogen and the isocyanide carbon atom. The intermediate in this reaction (i.e., **14**) contains an unusual and interesting six-membered-ring *N*-heterocyclic carbene moiety, and is about 15.1 kcal mol^{-1} higher in energy than **7**. No similar cyclization of an isocyanide to give such a rare six-membered *N*-heterocyclic carbene is known, to the best of our knowledge.[21] The calculated barrier for the ring-closure reaction is 16.9 kcal mol^{-1}. As final step, we propose a (probably intermolecular) proton shift to give **6a**, which is thermodynamically favoured (by about –22.6 kcal mol^{-1}) compared to **7**. These calculated data are in good agreement with the experimental conditions used.

We also considered a proton-catalysed route. It involves the initial protonation of **7** to give the nitrilium ion (i.e., **15**). A very exothermic cyclization reaction (by –43.2 kcal mol^{-1}) with a small barrier (only 1.9 kcal mol^{-1}) might lead to **16**, which, upon deprotonation from the methyl group, could produce **6a**. The exothermic nature and the low barrier of this pathway indicate that it should be a very attractive alternative to the neutral route. The neces-

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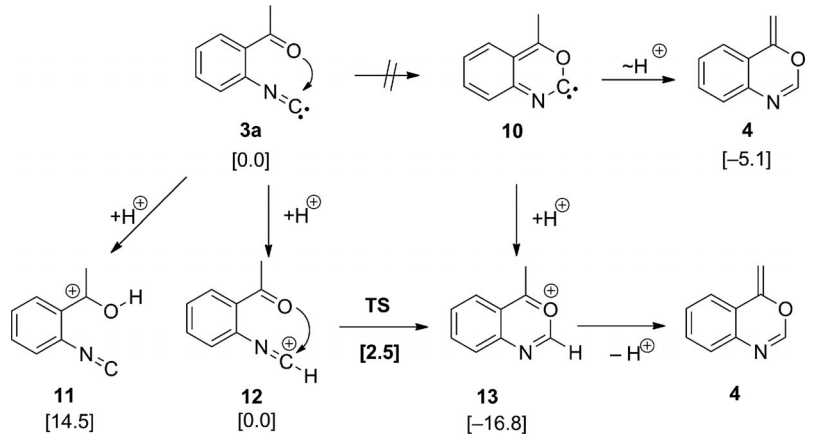
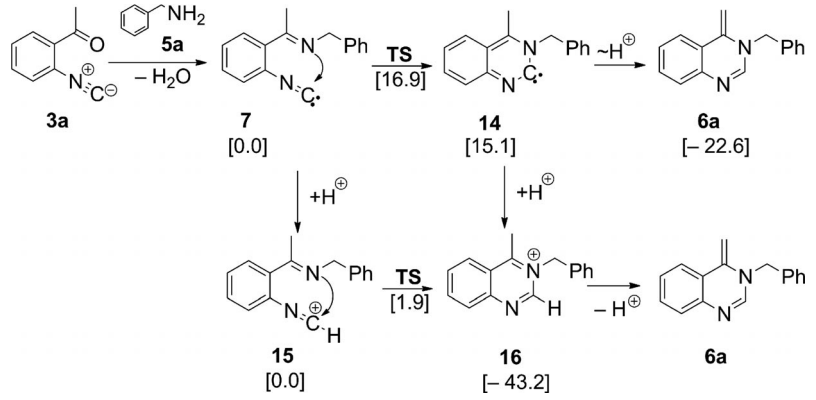


Scheme 5. Proposed mechanisms for the formation of compound **4** starting from isocyanide **3a**. Carbene **10** does not correspond to a minimum. The energies in upper line are relative to **3a**, those in the lower line are relative to **12** [kcal mol^{-1}], using SCS-MP2/6-311+G(d,p)//B3LYP/6-31+G(d)+ZPE. The zero point energies were taken from the DFT calculations.



Scheme 6. Proposed mechanisms for the formation of compound **6a** from the imine **7**. The energies in the first line are relative to **7**, those in the lower line are relative to **15** [kcal mol^{-1}], using SCS-MP2/6-311+G(d,p)//B3LYP/6-31+G(d)+ZPE. The zero point energies were taken from the DFT calculations.

sary catalytic protons may come from the molecular sieves under our experimental conditions.

Conclusions

2-Isocyanoacetophenone (**3a**) is a rather reactive substance. For example, it cyclizes intramolecularly in the presence of weak acids to form the hitherto unknown, rather unstable 4-methylene-4*H*-benzo[*d*][1,3]oxazine (**4**). This is the parent compound of various substituted derivatives known in the literature. Furthermore it has been found that reaction of compound **3a** with various benzylamines in the presence of molecular sieves leads to the unexpected formation of 3-benzyl-4-methylene-3,4-dihydroquinazolines **6a**–**e**. Surprisingly, imines **7** that would result from a condensation reaction were not observed. All compounds were completely characterized, and molecular structures of **6a** and **6d** were determined by X-ray diffraction. Compounds **6** were rapidly oxidized in air to give 3-(4-benzyl)-3*H*-quinazolin-4-one derivatives **9a** and **9d**. Thus, this method opens new pathways for the preparation of substituted 4-methylene-4*H*-benzo[*d*][1,3]oxazine (**4**) and quinazoline derivatives (such as **6**), their oxidation products **9**, and other related systems that might be of interest with regard to pharmacological and medicinal applications. We are now investigating the reactivity of the enamine functionality in compounds **6** and the suitability of these compounds for further modifications. In addition, we have investigated the mechanism for the formation of compounds **4** and **6** by quantum chemical calculations. The ring-closure reactions described here, which are likely to be induced by protonation, are rare examples of the use of isocyanides in the synthesis of six-membered heterocyclic rings. These results suggest that the synthesis of other heterocycles, e.g., with different ring sizes, could be achieved based on the mechanistic principles developed here.

Experimental Section

General Remarks: The following compounds were used as internal references in ^{1}H and ^{13}C NMR spectroscopy: Tetramethylsilane (^{1}H; δ = 0.00 ppm), CD_2Cl_2 (^{1}H; δ = 5.32 ppm), $CDCl_3$ (^{1}H; δ = 7.26 ppm), C_6D_6 (^{1}H; δ = 7.16 ppm), CD_2Cl_2 (^{13}C; δ = 53.8 ppm), $CDCl_3$ (^{13}C; δ = 77.0 ppm), C_6D_6 (^{13}C; δ = 128.1 ppm). If neces-

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sary, the experiments were carried out with the complete exclusion of moisture. For the synthesis of **2a**–**c** and **3a**,**b** modified literature procedures were used.[9] To the best of our knowledge, analytical data for **2c** are only partially reported in the literature.[10]

***N*-(2-Acetylphenyl)formamide (2a):** 2-Aminoacetophenone (13.50 mL, 111.10 mmol) was dissolved in toluene (50 mL) in a round-bottomed flask. Formic acid (41.88 mL, 1.11 mol) was added, and the mixture was heated at reflux for 4 h. The organic phase was washed carefully with $NaHCO_3$ (satd. aq.; 3× 50 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by recrystallization from cyclohexane/dichloroethane (1:1) to give **2a** (16.68 g, 102.20 mmol, 92%) as a colourless solid.

X-ray Crystal Structure Analysis of 2a:[11] Formula $C_9H_9NO_2$, M = 163.17, slightly yellow crystal, 0.20×0.10×0.10 mm, a = 14.1429(7), b = 3.8805(2), c = 15.5216(9) Å, β = 110.896(2)°, V = 795.82(7) Å^3, ρ_{calc} = 1.362 g cm^{-3}, μ = 0.097 mm^{-1}, empirical absorption correction ($0.981 \leq T \leq 0.990$), Z = 4, monoclinic, space group Pn (No. 7), λ = 0.71073 Å, T = 223(2) K, ω and ϕ scans, 4775 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin θ)/λ] = 0.67 Å^{-1}, 3142 independent (R_{int} = 0.036) and 2838 observed reflections [$I \geq 2\sigma(I)$], 227 refined parameters, R = 0.049, wR^2 = 0.116, max. (min.) residual electron density 0.17 (–0.16) e Å^{-3}, hydrogen atoms at N_{1A} and N_{1B} were refined freely, other hydrogen atoms were calculated and refined as riding atoms.

***N*-(2-Benzoylphenyl)formamide (2b):** Analogously to the synthesis of **2a**, 2-aminobenzophenone (0.56 g, 2.84 mmol) was dissolved in toluene (10 mL). Then formic acid (1.07 mL, 28.40 mmol) was added. After heating for 4 h under reflux, **2b** (0.36 g, 1.83 mmol, 64%) was obtained as a slightly yellow solid.

***N*-(2-Acetyl-4,5-dimethoxyphenyl)formamide (2c):** Analogously to the synthesis of **2a**, 1-(2-amino-4,5-dimethoxyphenyl)ethanone (5.00 g, 9.61 mL, 25.61 mmol) and formic acid (9.66 mL, 256.10 mmol) were mixed in toluene (100 mL). The mixture was heated for 4 h. The yellow precipitate was filtered and washed with diethyl ether (about 50 mL). The filtrate was neutralized and washed with $NaHCO_3$ as described for the synthesis of **2a**, to give **2c** (4.52 g, 20.23 mmol, 79%), m.p. 171 °C. IR (neat): $\tilde{\nu}$ = 3221 (w), 3204 (w), 3150 (vw), 3121 (vw), 2995 (w), 2970 (vw), 2941 (w), 2887 (w), 2841 (vw), 1684 (m), 1638 (m), 1611 (m), 1578 (m), 1520 (s), 1476 (m), 1458 (m), 1450 (m), 1410 (m), 1389 (m), 1366 (m), 1337 (m), 1254 (vs), 1204 (vs), 1173 (m), 1128 (m), 1053 (s), 1034 (m), 1018 (m) cm^{-1}. ^{1}H NMR (300.13 MHz, C_6D_6): δ = 2.04 (s, 3 H, CH_3), 3.35 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 6.82 (s, 1 H, C$H_{arom.}$), 7.87 (d, ^4J = 1.8 Hz, 1 H, C$H_{arom.}$), 8.81 (s, 1 H, CHO), 11.87 (br. s, 1 H, NH) ppm. ^{13}C NMR (C_6D_6, 75.47 MHz): δ = 27.9 (*C*H$_3$), 55.5 (O*C*H$_3$), 56.2 (O*C*H$_3$), 104.6 (*C*$_{arom.}$), 115.1 (*C*$_{arom.}$), 155.6 (*C*$_{ipso}$), 159.9 (*C*O) ppm. HRMS (ESI): calcd. for $C_{11}H_{13}NO_4Na$ 246.0737; found 246.0741.

X-ray Crystal Structure Analysis of 2c:[11] Formula $C_{11}H_{13}NO_4$, M = 223.22, yellow crystal 0.35× 0.27× 0.13 mm, a = 14.5534(4), b = 9.0344(3), c = 8.1465(2) Å, β = 97.135(2)°, V = 1062.82(5) Å^3, ρ_{calc} = 1.395 g cm^{-3}, μ = 0.107 mm^{-1}, empirical absorption correction ($0.964 \leq T \leq 0.986$), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 0.71073 Å, T = 223(2) K, ω and ϕ scans, 7810 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin θ) / λ] = 0.67 Å^{-1}, 2547 independent (R_{int} = 0.037) and 2212 observed reflections [$I \geq 2\sigma(I)$], 152 refined parameters, R = 0.049, wR^2 = 0.136, max. (min.) residual electron density 0.26 (–0.18) e Å^{-3}, the hydrogen atom at N_{11} was refined freely, other hydrogen atoms were calculated and refined as riding atoms.

1-(2-Isocyano-phenyl)ethanone (3a): A solution of $POCl_3$ (3.81 mL, 41.79 mmol) in dry THF (50 mL) was added dropwise to a mixture of compound **2a** (5.50 g, 33.70 mmol) and Et_3N (22.76 mL, 163.81 mmol) in dry THF (50 mL) at –78 °C. The mixture was stirred for 6 h at 0 °C, then it was poured into cold H_2O (50 mL). The mixture was extracted with diethyl ether (3× 50 mL), and the combined organic extracts were washed with H_2O (2× 50 mL) and dried with $MgSO_4$. Finally, the solvent was removed in vacuo to give **3a** (4.30 g, 29.62 mmol, 88%) as a dark brown oil. The product was sufficiently pure to be used in further reactions.

(2-Isocyanophenyl)(phenyl)methanone (3b): Analogously to the synthesis of **3a**, a solution of $POCl_3$ (1.13 mL, 12.40 mmol) in dry THF (50 mL) was added to a mixture of **2b** (2.25 g, 10.00 mmol) and Et_3N (6.78 mL, 48.60 mmol) in dry THF (50 mL). After 4 h at 0 °C, compound **3b** (0.23 g, 1.10 mmol, 11%) was obtained.

1-(2-Isocyano-4,5-dimethoxyphenyl)ethanone (3c): Analogously to the synthesis of **3a**, $POCl_3$ (3.85 mL, 42.16 mmol) was dissolved in dry THF (50 mL). This solution was added to a stirred solution of **2c** (7.59 g, 34.00 mmol) and Et_3N (23.05 mL, 165.24 mmol) in dry THF (50 mL). The reaction mixture was stirred overnight at room temperature. Compound **3c** (6.28 g, 30.60 mmol, 90%) was obtained as a brown solid, m.p. 115 °C. IR (neat): $\tilde{\nu}$ = 2120 (m), 1668 (m), 1639 (m), 1591 (m), 1512 (s), 1458 (m), 1449 (m), 1393 (m), 1362 (m), 1267 (s), 1260 (s), 1219 (s), 1146 (m), 1028 (m), 1022 (m) cm^{-1}. ^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 2.68 (s, 3 H, CH_3), 3.80 (s, 6 H, OCH_3), 6.91 (s, 1 H, C$H_{arom.}$), 7.28 (s, 1 H, C$H_{arom.}$) ppm. ^{13}C NMR (75.47 MHz, CD_2Cl_2): δ = 30.3 (*C*H$_3$), 56.7 (O*C*H$_3$), 56.9 (O*C*H$_3$), 111.9 (*C*H$_{arom.}$), 128.1, 150.0, 152.9, 169.9 (N*C*), 195.7 (*C*O) ppm. HRMS (ESI): calcd. for $C_{11}H_{12}NO_3$ 206.0812; found 206.0812.

4-Methylene-4*H*-benzo[*d*][1,3]oxazine (4): Compound **3a** (1.500 g, 15.17 mmol) was dissolved in dry toluene (15 mL) and treated with β-alanine (ca. 0.025 g) while stirring at room temperature. From this dark brown solution samples of 0.8 mL were taken. Toluene was removed from these samples in vacuo, and the residue was then dissolved in C_6D_6 for NMR measuements. Typical NMR spectra taken after 12, 48, and 140 h showed the conversion of **3a** into **4**, accompanied by increasing amounts of decomposition. NMR spectroscopic data after 10 d: ^{1}H NMR (C_6D_6, 300.13 MHz): δ = 4.40 (d, ^2J = 2.6 Hz, 1 H, CH_2), 4.52 (dd, ^2J = 2.6, ^5J = 1.1 Hz, 1 H, CH_2), 6.60 (d, ^5J = 1.1 Hz, 1 H, CH=N), 6.80 (ddd, 1 H), 6.90 (ddd, 1 H, C$H_{arom.}$), 7.10 (ddd, 1 H, C$H_{arom.}$), 7.20 (ddd, 1 H, C$H_{arom.}$) ppm. ^{13}C NMR (C_6D_6, 75.47 MHz): δ = 85.8 (*C*H$_2$), 122.5 (*C*$_{ipso}$), 122.9, 126.8, 128.1, 130.9 (*C*H$_{arom.}$), 138.1 (*C*$_{ipso}$), 148.5 (*C*H=N), 151.1 (*C*$_{quat.}$) ppm. For detailed spectra, see Supporting Information

General Procedure for the Synthesis of 3-Benzyl-4-methylene-3,4-dihydroquinazolines (6): Isocyanide **3a** (1.00 equiv.) was dissolved in dry CH_2Cl_2 in a Schlenk flask containing molecular sieves (4 Å). Then, amine (1.02 equiv.) was added. The solution was stirred at room temperature. After 18 h, the mixture was filtered through a pad of Celite, which was then washed with dry CH_2Cl_2 (3× 50 mL). The solvent was removed in vacuo, and the residue was recrystallized to give the pure product. To prevent oxidation to **8**, recrystallization was performed either by slow evaporation of solvent under vacuum or using an argon flow.

3-Benzyl-4-methylene-3,4-dihydroquinazoline (6a): Compound **3a** (0.25 g, 1.72 mmol) was dissolved in dry CH_2Cl_2 (50 mL). Then, benzylamine (0.20 mL, 1.76 mmol) was added to the stirred mixture. The solvent was removed in vacuo, and recrystallization from CH_2Cl_2 gave pure **6a** (0.30 g, 1.28 mmol, 75%) as an orange solid, m.p. 110–111 °C. IR (neat): $\tilde{\nu}$ = 3073 (vw), 3061 (vw), 3055 (vw),

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3032 (vw), 2997 (vw), 2988 (vw), 1692 (vw), 1676 (vw), 1624 (vs), 1603 (vs), 1593 (vs), 1572 (s), 1543 (w), 1522 (vw), 1489 (m), 1474 (m), 1454 (vs), 1425 (w), 1404 (m), 1383 (s), 1371 (vs), 1354 (s), 1333 (vw), 1315 (w), 1300 (w), 1275 (vw), 1261 (vw), 1225 (s), 1209 (m), 1175 (m), 1157 (w), 1148 (w), 1126 (w), 1115 (s), 1074 (w), 1057 (w), 1028 (w), 974 (s), 941 (vw), 922 (s), 903 (w), 853 (m), 800 (vw), 779 (s), 758 (vs), 750 (vs), 735 (vs), 700 (vs), 694 (vs), 667 (vw), 644 (vw), 625 (m), 610 (vw) cm^{-1}. ^1H NMR (CD_2Cl_2, 300.13 MHz): δ = 3.66 (d, ^3J = 3.0 Hz, 1 H, C$H_{2,olef.}$), 3.90 (s, 2 H, CH_2), 4.48–4.50 (m, 1 H, C$H_{2,olef.}$), 6.83–6.91 (m, 3 H, C$H_{arom.}$), 6.96 (s, 1 H, CH=N), 6.97–7.13 (m, 4 H, C$H_{arom.}$), 7.40 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1 H, C$H_{arom.}$), 7.62 (dd, ^3J = 7.8, ^4J = 1.2 Hz, 1 H, C$H_{arom.}$) ppm. ^{13}C NMR (C_6D_6, 75.47 MHz): δ = 53.4 (CH_2), 79.8 ($CH_{2,olef.}$), 123.0 ($CH_{arom.}$), 123.5 ($C_{quat.}$), 126.4, 126.5, 127.6, 127.8, 129.0, 130.3 ($CH_{arom.}$), 135.7, 140.2, 143.1 (C_{ipso}), 147.9 (CH=N) ppm. HRMS (ESI): calcd. for $C_{16}H_{14}N_2H$ 235.1230; found 235.1230. $C_{16}H_{14}N_2$ (234.30): calcd. C 82.02, H 6.02, N 11.96; found C 81.74, H 5.85, N 11.57.

X-ray Crystal Structure Analysis of 6a:[11] Formula $C_{16}H_{16}N_2$, M = 234.29, yellow crystal 0.30 × 0.25 × 0.25 mm, a = 9.680(1), b = 6.179(1), c = 20.601(3) Å, β = 92.94(1)°, V = 1230.6(3) Å^3, ρ_{calc} = 1.265 g cm^{-3}, μ = 0.583 mm^{-1}, empirical absorption correction (0.845 ≤ T ≤ 0.868), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, T = 223(2) K, ω and ϕ scans, 8219 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin θ) / λ] = 0.60 Å^{-1}, 2110 independent (R_{int} = 0.039) and 1902 observed reflections [$I \geq 2\sigma(I)$], 163 refined parameters, R = 0.046, wR^2 = 0.126, max. (min.) residual electron density 0.11 (–0.14) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

3-(4-Methylbenzyl)-4-methylene-3,4-dihydroquinazoline (6b): Compound **3a** (0.28 g, 1.90 mmol) was dissolved in dry CH_2Cl_2 (50 mL). Then, 4-methylbenzylamine (0.25 mL, 1.94 mmol) was added. Recrystallization from toluene gave **6b** (0.36 g, 1.46 mmol, 77%) as a pale orange solid, m.p. 91–92 °C. IR (neat): $\tilde{\nu}$ = 3049 (w), 3030 (w), 3013 (w), 3007 (w), 2924 (w), 2334 (w), 1674 (m), 1630 (m), 1607 (m), 1595 (s), 1566 (m), 1516 (m), 1485 (m), 1474 (m), 1462 (m), 1454 (m), 1396 (m), 1368 (s), 1312 (m), 1300 (m), 1273 (m), 1252 (m), 1223 (m), 1204 (m), 1182 (m), 1173 (m), 1155 (m), 1119 (m), 1103 (m), 1080 (m), 1038 (w), 1020 (m), 989 (w), 976 (w), 962 (m), 949 (m), 932 (m), 885 (w), 870 (w), 856 (m), 839 (w), 818 (m), 775 (s), 762 (s), 746 (vs), 698 (m), 669 (m), 662 (m), 652 (w), 640 (m), 627 (m), 611 (m), 592 (m), 583 (m), 571 (m), 563 (m), 552 (w), 546 (w), 538 (m), 528 (m), 511 (m) cm^{-1}. ^1H NMR (CD_2Cl_2, 300.13 MHz): δ = 2.34 (s, 3 H, CH_3), 3.82 (d, ^2J = 2.6 Hz, 1 H, C$H_{2,olef.}$), 4.58 (dd, ^2J = 2.6, ^5J = 0.9 Hz, 1 H, C$H_{2,olef.}$), 4.68 (s, 2 H, CH_2), 7.13–7.18 (m, 5 H, C$H_{arom.}$), 7.23–7.27 (m, 1 H, C$H_{arom.}$), 7.30–7.36 (m, 1 H, C$H_{arom.}$), 7.42 (s, 1 H, CH=N), 7.57 (dd, ^3J = 8.0, ^4J = 1.4 Hz, 1 H, C$H_{arom.}$) ppm. ^{13}C NMR (CD_2Cl_2, 75.47 MHz): δ = 21.3 (CH_3), 54.1 (CH_2), 80.0 ($CH_{2,olef.}$), 123.2 ($CH_{arom.}$), 123.5 ($C_{quat.}$), 126.7, 127.1, 127.2, 130.0, 130.5 ($CH_{arom.}$), 132.8, 138.2, 140.4, 142.7 (C_{ipso}), 148.5 (CH=N) ppm. HRMS (ESI): calcd. for $C_{17}H_{16}N_2H$ 249.1386; found 249.1372.

3-(4-Chlorobenzyl)-4-methylene-3,4-dihydroquinazoline (6c): Isocyanide **3a** (0.74 g, 5.00 mmol) was dissolved in dry CH_2Cl_2 (50 mL), and the mixture was stirred at room temp. Then, 4-chlorobenzylamine (0.63 mL, 5.17 mmol) was added. Recrystallization from CH_2Cl_2 gave **6c** (0.42 g, 1.55 mmol, 31%) as a colourless solid, m.p. 118–119 °C. IR (neat): $\tilde{\nu}$ = 3258 (w), 3219 (w), 2999 (w), 2984 (w), 2812 (w), 2803 (w), 1614 (vs), 1597 (vs), 1570 (vs), 1522 (w), 1491 (vs), 1481 (vs), 1458 (s), 1452 (s), 1437 (w), 1418 (w), 1402 (m), 1387 (vs), 1356 (vs), 1298 (w), 1281 (w), 1234 (m), 1227 (m), 1207 (s), 1190 (w), 1159 (vs), 1130 (s), 1090 (vs), 1074 (s), 1053 (m), 1036 (w), 1015 (vs), 976 (m), 955 (m), 934 (w), 922 (w), 858 (w), 826 (vs), 818 (vs), 800 (vs), 772 (vs), 764 (vs), 716 (vs), 689 (s), 665 (m), 633 (w), 608 (s) cm^{-1}. ^1H NMR (CD_2Cl_2, 400.13 MHz): δ = 3.75 (d, ^2J = 2.8 Hz, 1 H, C$H_{2,olef.}$), 4.58–4.59 (m, 1 H, C$H_{2,olef.}$), 4.70 (s, 2 H, CH_2), 7.16 (t, ^3J = 7.6 Hz, 1 H, C$H_{arom.}$), 7.23–7.35 (m, 6 H, C$H_{arom.}$), 7.41 (s, 1 H, CH=N), 7.57 (d, ^3J = 8.0 Hz, 1 H, C$H_{arom.}$) ppm. ^{13}C NMR (CD_2Cl_2, 100.61 MHz): δ = 46.2 (CH_2), 80.3 ($CH_{2,olef.}$), 123.2 ($C_{quat.}$), 126.8, 127.3, 128.6, 128.9, 129.1, 129.5, 130.6 ($CH_{arom.}$), 133.9, 134.6, 140.2, 142.5, 142.9 (C_{ipso}), 148.3 (CH=N) ppm. HRMS (ESI): calcd. for $C_{16}H_{13}ClN_2H$ 269.0840; found 269.0840.

3-(4-Methoxybenzyl)-4-methylene-3,4-dihydroquinazoline (6d): Compound **3a** (0.76 g, 5.20 mmol) was dissolved in dry CH_2Cl_2 (50 mL). Then, 4-methoxybenzylamine (0.69 mL, 5.30 mmol) was added. Recrystallization from CH_2Cl_2 gave **6d** (0.42 g, 1.60 mmol, 31%) as yellow crystals, m.p. 141–142 °C. IR (neat): $\tilde{\nu}$ = 3038 (vw), 3007 (w), 2955 (w), 2936 (vw), 2835 (vw), 2363 (w), 2342 (vw), 1630 (s), 1611 (m), 1595 (s), 1587 (m), 1562 (m), 1547 (m), 1533 (w), 1508 (s), 1477 (m), 1460 (s), 1441 (w), 1425 (w), 1404 (m), 1373 (s), 1364 (m), 1315 (m), 1292 (m), 1277 (w), 1238 (s), 1229 (s), 1206 (m), 1175 (s), 1152 (m), 1115 (w), 1101 (w), 1080 (w), 1055 (w), 1026 (m), 1011 (m), 980 (m), 962 (m), 928 (m), 910 (w), 887 (w), 878 (w), 856 (w), 837 (w), 816 (m), 779 (vs), 762 (vs), 746 (m), 712 (w), 696 (w), 687 (w), 669 (w), 650 (w), 627 (w), 608 (w) cm^{-1}. ^1H NMR (CD_2Cl_2, 300.13 MHz): δ = 3.78 (s, 3 H, OCH_3), 3.85 (d, ^2J = 2.7 Hz, 1 H, C$H_{2,olef.}$), 4.60 (dd, ^2J = 2.7, ^5J = 0.9 Hz, 1 H, C$H_{2,olef.}$), 4.65 (s, 2 H, CH_2), 6.87–6.92 (m, 2 H, C$H_{arom.}$), 7.13–7.27 (m, 4 H, C$H_{arom.}$), 7.30–7.34 (m, 1 H, C$H_{arom.}$), 7.34 (s, 1 H, CH=N), 7.58 (d, ^3J = 9.0 Hz, 1 H, C$H_{arom.}$) ppm. ^{13}C NMR (CD_2Cl_2, 75.48 MHz): δ = 53.6 (CH_2), 55.8 (OCH_3), 80.0 ($CH_{2,olef.}$), 114.7, 123.2 ($CH_{arom.}$), 123.5 ($C_{quat.}$), 126.6, 127.2 ($CH_{arom.}$), 127.6 (C_{ipso}), 128.5, ($CH_{arom.}$), 140.3, 142.6 (C_{ipso}), 148.4 (CH=N), 159.8 (C_{ipso}) ppm. HRMS (ESI): calcd. for $C_{17}H_{16}N_2OH$ 265.1335; found 265.1319.

X-ray Crystal Structure Analysis of 6d:[11] Formula $C_{17}H_{16}N_2O$, M = 264.32, yellow crystal 0.35 × 0.20 × 0.05 mm, a = 9.2898(2), b = 14.0573(4), c = 10.5040(3) Å, β = 94.694(1)°, V = 1367.11(6) Å^3, ρ_{calc} = 1.284 g cm^{-3}, μ = 0.081 mm^{-1}, empirical absorption correction (0.972 ≤ T ≤ 0.996), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 0.71073 Å, T = 223(2) K, ω and ϕ scans, 7577 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin θ) / λ] = 0.66 Å^{-1}, 3174 independent (R_{int} = 0.035) and 2501 observed reflections [$I \geq 2\sigma(I)$], 182 refined parameters, R = 0.061, wR^2 = 0.143, max. (min.) residual electron density 0.16 (–0.16) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

3-(2,4-Dimethoxybenzyl)-4-methylene-3,4-dihydroquinazoline (6e): Compound **3a** (1.02 g, 5.00 mmol) was dissolved in dry CH_2Cl_2 (50 mL). Then, 3,4-dimethoxybenzylamine (0.77 mL, 5.10 mmol) was added. Recrystallization from toluene/ethyl acetate gave **6e** (0.35 g, 1.20 mmol, 24%), m.p. 95 °C. IR (neat): $\tilde{\nu}$ = 2994 (w), 2947 (w), 2845 (w), 2835 (w), 1626 (m), 1603 (m), 1589 (m), 1572 (m), 1506 (m), 1485 (m), 1462 (m), 1435 (m), 1412 (m), 1385 (m), 1377 (m), 1306 (m), 1283 (m), 1269 (m), 1231 (m), 1209 (vs), 1194 (m), 1184 (m), 1161 (m), 1121 (m), 1103 (vs), 1078 (m), 1069 (w), 1038 (vs) cm^{-1}. ^1H NMR (400.13 MHz, CD_2Cl_2): δ = 3.78 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.91 (d, ^2J = 2.6 Hz, 1 H, CH=CH_2), 4.56 (m, 1 H, CH=CH_2), 4.61 (s, 2 H, CH_2), 6.44–6.46 (m, 1 H, C$H_{arom.}$), 6.50 (d, ^3J = 2.4 Hz, 1 H, C$H_{arom.}$), 7.08–7.15 (m, 2 H, C$H_{arom.}$), 7.29–7.22 (m, 1 H, C$H_{arom.}$), 7.28–7.32 (m, 1 H, C$H_{arom.}$), 7.39 (s, 1 H, CH=N), 7.56–7.58 (m, 1 H, C$H_{arom.}$) ppm. ^{13}C NMR (100.62 MHz, CD_2Cl_2): δ = 49.3 (CH_2), 55.9, 56.0 (OCH_3), 79.1 ($CH_{2,olef.}$), 99.0, 104.7 ($CH_{arom.}$), 115.4 ($C_{quat.,ipso}$), 123.2 ($CH_{arom.}$),

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123.5 ($C_{quat.,ipso}$), 126.4, 127.1, 129.6, 130.4 ($CH_{arom.}$), 140.6, 142.8 (C_{ipso}), 148.7 (*C*H=N), 159.1, 161.4 (C_{ipso}) ppm. HRMS (ESI): calcd. for $C_{18}H_{19}N_2O_2$ 295.1441; found 295.1437.

3-Benzylquinazolin-4(3*H*)-one (9a): Compound **6a** (0.30 g, 1.28 mmol) was stirred in ethyl acetate under air for 7 d. Subsequent recrystallization from the same solvent gave **9a** (0.08 g, 0.32 mmol, 25%) as yellow–orange crystals. The analytical data corresponds to the literature.[17]

3-(4-Methoxybenzyl)-3*H*-quinazolin-4-one (9d)

Procedure 1: Compound **6d** (0.26 g, 1.00 mmol) was stirred in ethyl acetate under air for 7 d. Subsequent recrystallization from the same solvent gave **9d** (0.05 g, 0.20 mmol, 20%) as orange crystals.

Procedure 2: A cyclohexane/ethyl acetate solution (1:1) of **6d** (0.42 g, 1.60 mmol) was filtered through a short silica column under air to allow the oxidation to take place. Compound **9d** (0.04 g, 0.16 mmol, 10%) was obtained as orange crystals. R_f [SiO_2, cyclohexane/ethyl acetate (1:1)]: 0.27, m.p. 123–124 °C. IR (neat): $\tilde{\nu}$ = 3069 (w), 3059 (w), 3034 (w), 3003 (w), 2982 (w), 2957 (w), 2930 (w), 2914 (w), 2837 (w), 2361 (vw), 2332 (vw), 1730 (w), 1663 (vs), 1607 (s), 1589 (m), 1570 (m), 1562 (m), 1510 (s), 1485 (m), 1472 (s), 1454 (m), 1447 (m), 1437 (m), 1422 (m), 1408 (m), 1389 (m), 1366 (s), 1356 (m), 1323 (m), 1312 (m), 1292 (s), 1244 (vs), 1202 (m), 1182 (s), 1165 (s), 1140 (m), 1103 (m), 1026 (s), 986 (m), 970 (m), 957 (m), 924 (m), 874 (m), 839 (m), 820 (s), 812 (s), 800 (m), 781 (m), 768 (vs), 748 (s), 716 (m), 692 (s), 664 (m), 656 (m), 633 (m), 608 (m) cm^{-1}. ^1H NMR (CD_2Cl_2, 400.13 MHz): δ = 3.77 (s, 3 H, CH_3), 5.10 (s, 2 H, CH_2), 6.85–6.90 (m, 2 H, C$H_{arom.}$), 7.29–7.33 (m, 2 H, C$H_{arom.}$), 7.47–7.51 (m, 1 H, C$H_{arom.}$), 7.66–7.69 (m, 1 H, C$H_{arom.}$), 7.72–7.77 (m, 1 H, C$H_{arom.}$), 8.11 (s, 1 H, C*H*=N), 8.26–8.29 (m, 1 H, C$H_{arom.}$) ppm. ^{13}C NMR (CD_2Cl_2, 100.61 MHz): δ = 49.7 (O*C*H_3), 55.8 (*C*H_2), 114.7 (*C*$H_{arom.}$), 122.9 ($C_{quat.}$), 127.1, 127.7, 128.0 (*C*$H_{arom.}$), 128.7 (C_{ipso}), 130.1, 134.6 (*C*$H_{arom.}$), 147.1 (*C*H=N), 148.8, 160.1, 161.4 ($C_{quat.,ipso}$) ppm. HRMS (ESI): calcd. for $C_{16}H_{14}N_2O_2H$ 267.1128; found 267.1129. $C_{16}H_{14}N_2O_2$ (266.29): calcd. C 72.16, H 5.30, N 10.52; found C 71.99, H 5.59, N 10.14.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of new compounds; total energies (SCS-MP2/6-311+G(d,p)//B3LYP/6-31+G(d)+ZPE), Cartesian coordinates (B3LYP/6-31+G(d))//B3LYP/6-31+G(d)), and numbers of imaginary frequencies for the calculated structures; and graphical plots of the crystal structures.

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