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Reactions of 2-Unsubstituted 1*H*-Imidazole 3-Oxides with Heterocumulenes and Dimethyl Acetylenedicarboxylate

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Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

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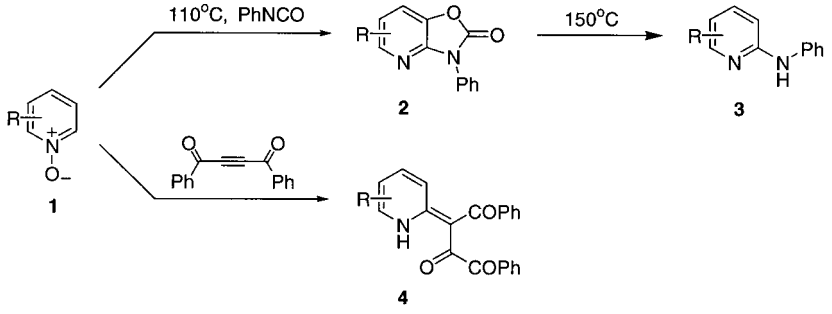
Abstract—Reaction of 2-unsubstituted 1*H*-imidazole 3-oxides with isocyanates, isothiocyanates, and dimethyl acetylenedicarboxylate led to the formation of 2-functionalized imidazole derivatives. Stepwise reaction mechanisms via zwitterionic intermediates are proposed. The intermediate [3+2] cycloadducts stabilize via extrusion of COX or ring opening.

Introduction

In contrast to other azaheterocyclic *N*-oxides, imidazole *N*-oxides cannot be prepared by oxidation of the parent compound.[1,2] However, syntheses based on condensation reactions with α-hydroxyimino ketones and imines[3] or 1,2-diimines and oximes[4] were recently developed which offered an easy access to differently substituted imidazole *N*-oxides. In the case of unsubstituted C(2), they can conveniently be exploited for the preparation of C(2)-functionalized derivatives. Thus, photolysis in methanolic solution afforded imidazol-2-ones,[5] cyanation using trimethylsilanecarbonitrile (Me_3SiCN) led to imidazole-2-carbonitriles,[6,7] and chlorination with $POCl_3$ yielded 2-chloroimidazoles.[8]

Formally, imidazole *N*-oxides contain the structural fragment of a 1,3-dipole which is comparable with nitrones. Therefore, they are expected to undergo [3+2] cycloadditions with suitable dipolarophiles. In the case of other aza-aromatic *N*-oxides, this type of reaction is well established. E.g. pyridine *N*-oxides **1** react with phenyl isocyanate at 110°C to give oxazolo[4,5-*b*]pyridines **2** which, at 150°C, extrude CO_2 to give 2-aminopyridines **3** (Scheme 1).[9] The reaction of **1** with dibenzoylacetylene occurs smoothly at room temperature leading to 2-substituted pyridine derivatives **4**.[10] The structures of the isolated products **2** and **4** show that the primarily formed [3+2] cycloadducts undergo fast secondary reactions. Several examples of similar transformations with pyridine, quinoline, and isoquinoline *N*-oxides have been reviewed recently.[11] The isolation of the initial cycloadduct was achieved in the case of the reaction of dimethyl acetylenedicarboxylate and a quinoxaline 4-oxide.[12]

Reactions of *N*-oxides of five-membered aromatic azaheterocycles including imidazole *N*-oxides are rarely



Scheme 1.

Keywords: imidazole *N*-oxides; isocyanates; isothiocyanates; acetylenedicarboxylate; [3+2] cycloadducts.
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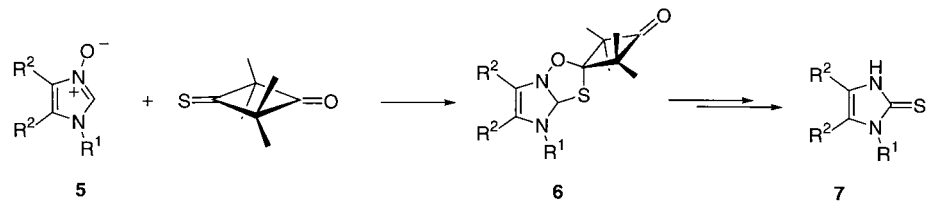


Scheme 2.

reported. A study of the reaction of 2-unsubstituted imidazole *N*-oxides **5** with cycloaliphatic thioketones leading to the corresponding imidazole-2-thiones **7** was published two years ago (Scheme 2).[3] The proposed reaction mechanism involves the formation of the [3+2] cycloadduct **6** which spontaneously eliminates 2,2,4,4-tetramethylcyclobuta-1,3-dione. This reaction is clear-cut evidence for the 'nitrone-like' 1,3-dipolar reactivity of **5**.

To the best of our knowledge, the only other examples of 1,3-dipolar cycloadditions of **5** were reported by Ferguson and Schofield.[8] Their study was limited to one reaction with phenyl isocyanate and dimethyl acetylenedicarboxylate, respectively, and 1-benzyl-4,5-dimethyl-1*H*-imidazole 3-oxide (**5**, R^1=$PhCH_2$, R^2=R^3=Me). The isolated products were described as 2-substituted imidazole derivatives similar to those obtained with pyridine 1-oxide (i.e. **3** and **4**).

The aim of the present study was to determine the scope and limitations of [3+2] cycloadditions using imidazole *N*-oxides **5**. Attempted reactions with different dipolarophiles showed that isocyanates, isothiocyanates, and acetylenedicarboxylates are the most promising reagents.

Results and Discussion

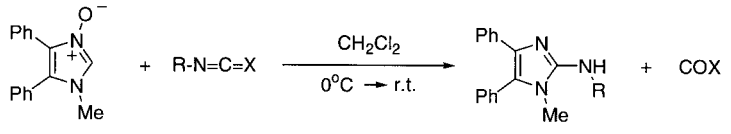
In order to test the reactivity of aliphatic isocyanates towards imidazole *N*-oxides, we selected cyclohexyl isocyanate (**8a**) and 1-methyl-4,5-diphenyl-1*H*-imidazole 3-oxide (**5a**) as reaction partners. Equimolar amounts of the components were dissolved in dichloromethane at 0°C, and the mixture was stirred at room temperature for 20 h. The crude reaction mixture was examined by ^{1}H NMR spectroscopy which indicated the presence of only one major product. Crystallization from methanol afforded 2-(cyclohexylamino)imidazole **9a** in 68% yield, which was identified by elemental analysis and spectroscopic data (Scheme 3). The analogous reaction course was observed with **5a** and butyl isocyanate (**8b**); in this case, the smooth reaction led to **9b** in 65% yield. Finally, we attempted to react **5a** with (*tert*-butyl) isocyanate. Although the reaction time was extended to 3 days, no addition product could be detected.

Under the same reaction conditions (dichloromethane, room temperature) cyclohexyl isothiocyanate (**8c**), butyl isothiocyanate (**8d**), and methyl isothiocyanate (**8e**) reacted similarly as the corresponding isocyanates to give **9a**–**c** (Scheme 3). The molecular structure of **9c** was established by X-ray crystallography (Fig. 1). The NH group forms an intermolecular H-bond with the unsubstituted N-atom of the imidazole ring of a neighboring molecule. The H-bonds link the molecules into infinite one-dimensional chains running parallel to the *z*-axis.

Unexpectedly, 2-amino-imidazoles **9a**–**c** were not converted into thiourea derivatives under the reaction conditions. Similarly, in the case of the reactions with isocyanates **8a**,**b**, urea derivatives were formed neither with equimolar amounts of **5a** and **8a**,**b** nor with a twofold excess of **8a**.

In contrast to reactions with **8a**, phenylisocyanate and 1-methyl-4,5-diphenyl-1*H*-imidazole 3-oxide (**5a**) yielded two different products depending on the ratio of the reagents. Whereas in the experiment with equimolar amounts the only product was 1-methyl-4,5-diphenyl-2-(phenylamino)imidazole (**9d**), the reaction with excess phenyl isocyanate led to urea derivative **10a** (Scheme 4). In an additional experiment, **9d** was transformed into **10a** by treatment with phenyl isocyanate at room temperature.

With imidazole *N*-oxides **5b**,**c** the reactions were carried out using excess phenyl isocyanate (ratio 1:2), and the urea derivatives **10b** and **10c**, respectively, were obtained as the sole products. The formation of **10b** deserves a comment as Ferguson and Schofield[8] reported on the same reaction. A crystalline solid with a melting point of 237–238°C was



5a

8a R = C_6H_{11}, X = O
b R = *n*-Bu, X = O
c R = C_6H_{11}, X = S
d R = *n*-Bu, X = S
e R = Me, X = S

9a R = C_6H_{11}
b R = *n*-Bu
c R = Me

Scheme 3.

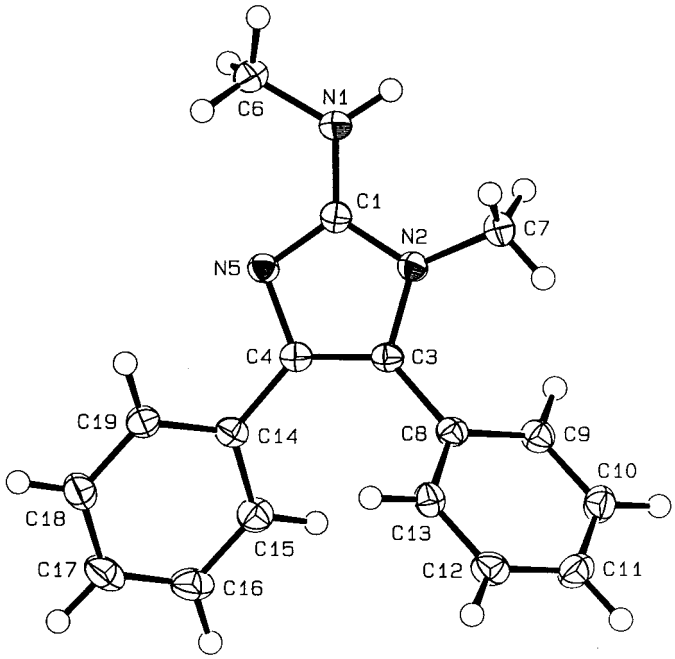


Figure 1. ORTEP-Plot[13] of the molecular structure of **9c** (arbitrary numbering of atoms, 50% probability ellipsoids; H-atoms given arbitrary displacement parameters for clarity).

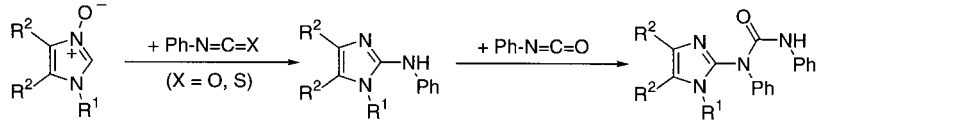
believed to possess structure **10b**. The substance in our hands, fully characterized by elemental analysis and spectral data (MS, ^{1}H and ^{13}C NMR, IR), melted at 157–158°C.[‡]

In analogy to the reactions of **5** with aliphatic isothiocyanates, treatment of **5a**, **b**, and **d**, respectively, with phenyl isothiocyanate afforded imidazoles **9d**, **e**, and **f** as the sole products. An attempted conversion of the isolated **9d** to the corresponding thiourea derivative with an excess of phenyl isothiocyanate at room temperature was in vain.

Another dipolarophile, which easily enters reactions with imidazole *N*-oxides **5**, was dimethyl acetylenedicarboxylate (DMAD).[§] The reactions with **5b–e** were carried out in chloroform at 0°C, and they were complete after 1 h. In all cases, only one product was obtained and identified as butanedioate **11** (Scheme 5). The structures were confirmed by their spectral data; e.g. the IR spectrum (KBr) of **11a** shows three (C=O) absorptions at 1720, 1670, and

[‡] Imidazole *N*-oxides are difficult to obtain free of water. Therefore, one can expect that the reaction with phenyl isocyanate can lead to considerable amounts of *N,N'*-diphenylurea (carbanilide, mp 238–240°C).

[§] Phenylacetylene was shown to be unreactive under these conditions.

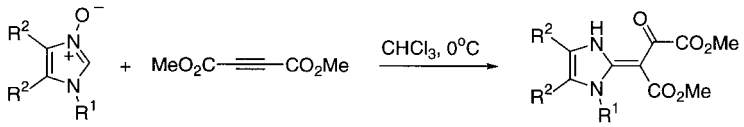


5a R^1 = Me, R^2 = Ph
b R^1 = Ph-CH_2, R^2 = Me
c R^1 = C_6H_{11}, R^2 = Me
d R^1 = C_6H_{11}, R^2 = Ph

9d R^1 = Me, R^2 = Ph
e R^1 = Ph-CH_2, R^2 = Me
f R^1 = C_6H_{11}, R^2 = Ph

10a R^1 = Me, R^2 = Ph
b R^1 = Ph-CH_2, R^2 = Me
c R^1 = C_6H_{11}, R^2 = Me

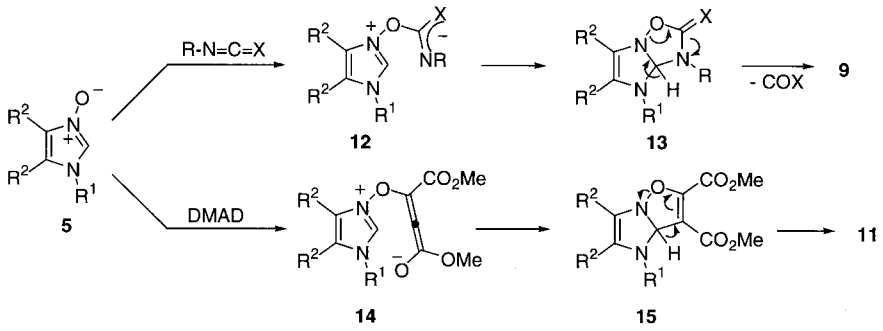
Scheme 4.



5b R^1 = Ph-CH_2, R^2 = Me
c R^1 = C_6H_{11}, R^2 = Me
d R^1 = C_6H_{11}, R^2 = Ph
e R^1 = R^2 = Me

11a R^1 = Ph-CH_2, R^2 = Me
b R^1 = C_6H_{11}, R^2 = Me
c R^1 = C_6H_{11}, R^2 = Ph
d R^1 = R^2 = Me

Scheme 5.



Scheme 6.

1650 cm^{-1} and in the ^{13}C NMR spectrum ($CDCl_3$) three signals for (C=O) groups appeared at 208.7, 168.4 and 167.8 ppm. The signals of C(2) and the methylidene-C atom were found at 143.7 and 80.9 ppm, respectively.

The mechanistic interpretation of the reactions leading to **9** and **11** is based on the assumption that cycloadducts **13** and **15**, respectively, are the precursors. The formation of **13** and **15**, which formally are [3+2] cycloadducts of **5** and the dipolarophiles, is expected to occur stepwise via the primarily formed zwitterionic intermediates **12** and **14**, respectively. This proposal is supported by the fact that isocyanates and isothiocyanates gave the same products **9**.[‖] In the case of isothiocyanates, zwitterion **12** should form the five-membered ring via attack of the more nucleophilic S-atom. As the elimination of COS to give **9** requires 1,2,4-oxadiazolidine-5-thione **13** (X=S) as an appropriate precursor, an equilibrium between the initially formed 1,4,2-oxathiazolidin-5-imine and **12** has to be postulated. The driving force of the COX elimination from **13** is the stability of the extruded molecule and the aromatization of the imidazole ring. Similarly, stabilization of **15** occurs via cleavage of the weak N–O bond and formation of the conjugated, 'push–pull-stabilized' product **11**. Additionally, **11** is stabilized by an intramolecular H-bond between NH and the ketone O-atom indicated by the down-field shift of the NH absorption (δ(NH) in **11b**: 12.35 ppm) (Scheme 6).

Considering the above interpretation, unsuccessful experiments with other dipolarophiles, known to be good reaction partners in cycloaddition reactions with nitrones,[15] can be plausibly explained.

In contrast to **5**, non-aromatic imidazole N-oxides[16] behave like nitrones in reactions with DMAD and form stable [3+2] cycloadducts **17**[16] (Scheme 7; cf. also Ref. 17).

[‖] Generally, 1,3-dipolar cycloadditions with isocyanates and isothiocyanates lead to different products. Whereas in the case of isocyanates addition onto the C=N bond is observed, isothiocyanates react preferably at the C=S bond.[14]

Experimental

Melting points were determined in a capillary using a Melt-Temp (Aldrich) or Büchi-510 apparatus and are uncorrected. IR Spectra: Specord-71 IR and Perkin–Elmer FT-IR-1600 spectrometers; in KBr. ^1H and ^{13}C NMR Spectra: Varian-Gemini-BB spectrometer (200 MHz for ^1H and 50.4 MHz for ^{13}C) or Bruker ARX-300 (300 MHz for ^1H and 75.5 MHz for ^{13}C); $CDCl_3$ solutions; other solvents are given in parentheses; TMS was used as an internal standard (δ(TMS)=0 ppm). EI-MS: Varian-MAT-112S spectrometer; at 70 eV; CI-MS with NH_3.

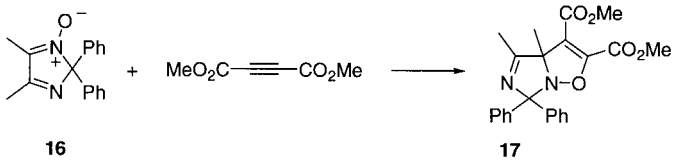
Starting materials

The 1*H*-imidazole 3-oxides **5** were prepared by condensation of the corresponding hexahydro-1,3,5-triazines and α-hydroxyimino ketones following a known protocol.[3] Phenyl isocyanate, phenyl isothiocyanate as well as isocyanates **8a**, **b** and isothiocyanates **8c–e** were commercially available reagents purchased from Aldrich or Fluka.

Reactions of 1-methyl-4,5-diphenyl-1*H*-imidazole 3-oxide (5a) with isocyanates 8a,b and phenyl isocyanate (molar ratio 1:1)

General procedure: A solution of 767 mg (3 mmol) of **5a** in 6 ml of abs. dichloromethane was cooled in a water/ice bath. The solution was stirred magnetically and 3 mmol of freshly distilled isocyanate dissolved in 6 ml of dichloromethane were added dropwise at such a rate that the temperature did not exceed 5°C. When the addition was complete, the bath was removed and the stirring was continued at room temperature for 20 h. Then, the solvent was evaporated under vacuum and the crude products were purified by recrystallization. Reported yields refer to recrystallized products.

2-Cyclohexylamino-1-methyl-4,5-diphenylimidazole (9a). With cyclohexyl isocyanate (**8a**; 375.3 mg, 3 mmol). Colorless crystals with mp 135–136°C (hexane/dichloromethane);



Scheme 7.

yield: 676 mg (68%). IR: 2925*s*, 2852*s*, 1574*vs*, 1526*s*, 1031*s*, 774*s*, 704*s*. ^{1}H NMR: 7.47–7.05 (*m*, 10 arom. H); 3.75–3.70 (*m*, CHN); 3.20 (*s*, CH_3N); 2.21–2.16, 1.86–1.12 (2*m*, 5 CH_2). ^{13}C NMR: 148.9, 134.9, 133.0, 131.3, 124.5 (5*s*, C(2), C(4), C(5), 2 arom. C); 130.7, 128.7, 127.8, 127.7, 126.7, 125.6 (6*d*, 10 arom. CH); 52.6 (*d*, CHN); 34.0, 25.8, 24.9 (3*t*, 5 CH_2); 29.6 (*q*, CH_3N). CI-MS: 333 (22), 332 (100, $[M+1]^+$), 261 (17), 228 (16). Anal. Calcd for $C_{22}H_{25}N_3$ (331.46): C 79.72, H 7.60, N 12.68; found: C 79.64, H 7.50, N 12.64.

2-Butylamino-1-methyl-4,5-diphenylimidazole (9b). With butyl isocyanate (**8b**; 297.4 mg, 3 mmol). Colorless crystals with mp 189–191°C (hexane/dichloromethane); yield: 596 mg (65%). IR: 3325*s*, 2949*s*, 1567*vs*, 766*s*, 700*vs*. ^{1}H NMR (DMSO-d_6): 8.58–8.52 (*m*, NH); 7.52–7.22 (*m*, 10 arom. H); 3.58–3.52 (*m*, CH_2N); 3.31 (*s*, CH_3N); 1.72–1.60, 1.49–1.37 (2*m*, 2 CH_2); 0.95 (*t*, CH_3). ^{13}C NMR (DMSO-d_6): 146.6, 127.4, 126.7, 124.6, 122.4 (5*s*, C(2), C(4), C(5), 2 arom. C); 130.8, 130.5, 129.6, 129.1, 128.3, 127.6 (6*d*, 10 arom. CH); 42.7 (*t*, CH_2N); 30.8, 19.2 (2*t*, 2 CH_2); 30.7 (*q*, CH_3N); 13.6 (*q*, CH_3). CI-MS: 307 (19), 306 (100, $[M+1]^+$). Anal. Calcd for $C_{20}H_{23}N_3$ (305.42): C 78.65, H 7.59, N 13.76; found: C 78.55, H 7.65, N 13.70.

1-Methyl-4,5-diphenyl-2-(phenylamino)imidazole (9d). With phenyl isocyanate (357.4 mg, 3 mmol). Colorless crystals with mp 222–224°C (hexane/dichloromethane); yield: 508 mg (52%). IR: 3175*s*, 3056*m*, 2930*m*, 1603*vs*, 1526*vs*, 1496*vs*, 1457*vs*, 1440*s*, 1380*vs*, 1256*s*, 780*vs*, 749*vs*, 720*vs*, 698*vs*. ^{1}H NMR (DMSO-d_6): 8.50 (*s*, NH); 7.58–7.38, 7.29–7.06, 6.87–6.82 (3*m*, 15 arom. H); 3.30 (*s*, CH_3N). ^{13}C NMR (DMSO-d_6): 144.2, 142.6, 134.8, 132.0, 130.8, 124.8 (6*s*, C(2), C(4), C(5), 3 arom. C); 130.6, 128.9, 128.6, 128.2, 127.8, 125.8, 125.6, 119.5, 116.0 (9*d*, 15 arom. CH); 30.6 (*q*, CH_3N). CI-MS: 326 (100, $[M+1]^+$). Anal. Calcd for $C_{22}H_{19}N_3$ (325.41): C 81.20, H 5.89, N 12.91; found: C 81.08, H 6.31, N 12.95.

Reactions of 5a with a two-fold molar amount of 8a,b

A solution of 367 mg (3 mmol) of **5a** in 6 ml of abs. dichloromethane was treated with 6 mmol of **8a** and **8b**, respectively, according to the previous protocol. After 3 days, the solvent was evaporated under vacuum and the residues were analyzed by ^{1}H NMR spectroscopy. The only products were 2-aminoimidazoles **9a** and **9b**, respectively.

Reactions of 1*H*-imidazole 3-oxides 5a–c with a two-fold molar amount of phenyl isocyanate

General procedure: A stirred solution of 3 mmol of respective **5** in 6 ml of abs. dichloromethane was cooled in a water/ice bath and a solution of 715 mg (6 mmol) of freshly distilled phenyl isocyanate in 6 ml of abs. dichloromethane was added in portions, whereby the temperature of the mixture was kept at 0–5°C. After complete addition, the cooling bath was removed and the solution was stirred at room temperature for 3 days. Evaporation of the solvent under vacuum afforded solid residues which were purified by recrystallization. The stated yields refer to pure compounds **10**.

***N*-(1-Methyl-4,5-diphenylimidazol-2-yl)-*N*,*N*′-diphenylurea (10a).** With **5a** (750.9 mg, 3 mmol). Colorless crystals with mp 157–158°C (hexane/ethyl acetate); yield: 920 mg (69%). IR: 1702*vs* (C═O), 1600*vs*, 1526*vs*, 1496*vs*, 1442*vs*, 1401*s*, 1311*s*, 1274*vs*, 1234*vs*, 760*s*, 741*s*, 693*vs*. ^{1}H NMR: 8.71 (*s*, NH); 7.56–7.39, 7.36–7.15, 7.09–7.04 (3*m*, 20 arom. H); 3.12 (*s*, CH_3N). ^{13}C NMR: 152.4 (*s*, C═O); 142.0, 139.7, 138.2, 135.3, 133.9, 130.2, 128.6 (7*s*, C(2), C(4), C(5), 4 arom. C); 129.2, 129.0, 128.9, 128.2, 126.6, 126.5, 123.5, 119.7 (8*d*, 20 arom. CH); 31.2 (*q*, CH_3N). EI-MS: 325 (24), 324 (100, $[(M+1)-C_6H_5NHCO]^+$), 323 (30), 309 (7), 234 (5), 197 (7), 193 (12), 186 (5), 119 (32), 91 (8). Anal. Calcd for $C_{29}H_{24}N_4O$ (444.54): C 78.35, H 5.44, N 12.60; found: C 78.14, H 5.63, N 12.60.

***N*-(1-Benzyl-4,5-dimethylimidazol-2-yl)-*N*,*N*′-diphenylurea (10b).** With 1-benzyl-4,5-dimethylimidazole 3-oxide (**5b**; 606.8 mg, 3 mmol). Colorless crystals with mp 120–122°C (hexane/tetrachloromethane); yield: 405 mg (34%). IR: 1675*vs* (C═O), 1597*vs*, 1542*vs*, 1497*vs*, 1443*vs*, 1315*vs*, 1246*vs*, 754*s*, 692*s*. ^{1}H NMR: 7.61 (*s*, NH); 7.47–7.13, 7.05–7.00, 6.88–6.85 (3*m*, 15 arom. H); 4.85 (*s*, CH_2N); 2.24, 2.02 (2*s*, 2 CH_3). ^{13}C NMR: 152.8 (*s*, C═O); 139.8, 139.4, 135.8, 132.0, 123.1 (5*s*, C(2), C(4), C(5), 3 arom. C); 129.0, 128.7, 127.5, 126.3, 126.1, 123.5, 120.0 (7*d*, 15 arom. CH); 46.9 (*t*, CH_2N); 12.7, 9.0 (2*q*, 2 CH_3). CI-MS: 397 (15, $[M+1]^+$), 278 (100), 213 (15). Anal. Calcd for $C_{25}H_{24}N_4O$ (396.49): C 75.73, H 6.10, N 14.13; found: C 75.54, H 6.02, N 14.05.

***N*-(1-Cyclohexyl-4,5-dimethylimidazol-2-yl)-*N*,*N*′-diphenylurea (10c).** With 1-cyclohexyl-4,5-dimethylimidazole 3-oxide (**5c**; 582.8 mg, 3 mmol). Colorless crystals with mp 168–170°C (after chromatography on a silica gel column with dichloromethane/ethyl acetate 8:2 and recrystallization from diethyl ether/dichloromethane); yield: 583 mg (50%). IR: 3340*s*, 2930*vs*, 1690*vs* (C═O), 1590*vs*, 1490*vs*, 1443*vs*, 1440*vs*, 1305*s*, 1260*vs*, 1210*vs*, 745*s*, 690*s*. ^{1}H NMR: 7.49 (*s*, NH); 7.45–6.95 (*m*, 10 arom. H); 4.02–3.98 (*m*, CHN); 2.22, 2.19 (2*s*, 2 CH_3); 1.80–1.00 (*m*, 5 CH_2). ^{13}C NMR: 153.1 (*s*, C═O); 141.0, 138.3, 133.1, 122.5, 118.1 (5*s*, C(2), C(4), C(5), 2 arom. C); 128.8, 125.9, 125.4, 123.5, 120.0 (5*d*, 10 arom. CH); 56.5 (*d*, CHN); 31.4, 26.2, 25.2 (3*t*, 5 CH_2); 12.7, 10.8 (2*q*, 2 CH_3). EI-MS: 388 (7, $M^{+\cdot}$), 270 (43), 269 (100), 268 (12), 188 (47), 187 (100), 186 (100), 171 (8), 119 (45), 111 (18). Anal. Calcd for $C_{24}H_{28}N_4O$ (388.51): C 74.20, H 7.26, N 14.42; found: C 74.06, H 7.18, N 14.37.

Reactions of 1*H*-imidazole 3-oxides 5a–c with phenyl isothiocyanate

General procedure: To a stirred, cooled solution (water/ice bath) of 3 mmol of respective **5** in 6 ml of abs. dichloromethane were added in small portions 405 mg (3 mmol) phenyl isothiocyanate dissolved in 6 ml of abs. dichloromethane. After 20 h at room temperature, the solvent was evaporated under vacuum and crude products **9** were purified either by chromatography or recrystallization.

1-Methyl-4,5-diphenyl-2-(phenylamino)imidazole (9d). With **5a** (750.9 mg, 3 mmol). Crystallization from hexane/dichloromethane; mp 222–223.5°C. Yield: 839 mg (86%).

All spectral data were identical with those of the sample of **9d** obtained from the reaction with phenyl isocyanate.

1-Benzyl-4,5-dimethyl-2-(phenylamino)imidazole (9e). With **5b** (606.8 mg, 3 mmol). Chromatography on silica gel with hexane/ethyl acetate 1:1 and recrystallization from hexane/dichloromethane; colorless crystals with mp 111.5–113°C; yield: 483 mg (58%). IR: 3029*s*, 2935*s*, 2914*s*, 1599*vs*, 1561*vs*, 1526*vs*, 1497*vs*, 1474*s*, 1447*s*, 1398*vs*, 1348*s*, 1306*s*, 1252*s*, 750*s*, 730*s*, 717*s*, 696*s*. ^{1}H NMR: 7.33–7.14, 7.02–6.99, 6.86–6.81, 6.79–6.76 (4*m*, 10 arom. H); 5.41 (*s*, NH); 4.92 (*s*, CH_2N); 2.17, 2.05 (2*s*, 2 CH_3). ^{13}C NMR: 144.3, 144.0, 141.3, 136.7, 130.5 (5*s*, C(2), C(4), C(5), 2 arom. C); 129.1, 128.8, 127.5, 126.1, 120.1, 115.1 (6*d*, 10 arom. CH); 46.3 (*t*, CH_2N); 12.6, 9.0 (2*q*, 2 CH_3). EI-MS: 278 (13), 277 (68, $M^{+\cdot}$), 226 (6), 187 (12), 186 (100, $[M-C_6H_5N]^+$), 183 (6). Anal. Calcd for $C_{18}H_{19}N_3$ (277.37): C 77.94, H 6.90, N 15.15; found: C 77.36, H 7.08, N 15.03.

1-Cyclohexyl-4,5-diphenyl-2-(phenylamino)imidazole (9f). With 1-cyclohexyl-4,5-diphenylimidazole 3-oxide (**5d**; 955.3 mg, 3 mmol). Crystallization from hexane/dichloromethane; colorless crystals with mp 139–140°C; yield: 956 mg (81%). IR: 2940*vs*, 1605*vs*, 1525*vs*, 1500*vs*, 1460*vs*, 1400*m*, 1380*s*, 1300*s*, 1270*s*, 770*s*, 700*vs*. ^{1}H NMR: 7.46–6.83 (*m*, 15 arom. H); 3.77–3.73 (*m*, CHN); 1.91–1.49, 1.15–0.93 (2*m*, 5 CH_2). ^{13}C NMR: 145.0, 142.7, 137.4, 134.8, 134.6, 131.9 (6*s*, C(2), C(4), C(5), 3 arom. C); 131.6, 128.9, 128.7, 127.9, 126.8, 126.0, 125.3, 120.1, 115.6 (9*d*, 15 arom. CH); 56.3 (*d*, CHN); 32.4, 26.1, 25.1 (3*t*, 5 CH_2). CI-MS: 394 (8, $[M+1]^+$), 393 (24, $M^{+\cdot}$), 303 (21), 302 (93), 220 (52), 219 (55), 193 (7), 165 (17), 93 (100), 77 (14). Anal. Calcd for $C_{27}H_{27}N_3$ (393.53): C 82.41, H 6.92, N 10.68; found: C 81.82, H 7.22, N 10.67.

Reactions of 5a with two-fold molar amount of isothiocyanates 8c–e

In analogy to the reactions with isocyanates, solutions of 367 mg (3 mmol) of **5a** in 6 ml of abs. dichloromethane were reacted with 2 equiv. of **8c–e**. After stirring for 20 h at room temperature, evaporation of the solvent afforded crude 2-aminoimidazoles **9a–c**. In the cases of **8c** (847.4 mg, 6 mmol) and **8d** (691.2 mg, 6 mmol), *2-cyclohexylamino-1-methyl-4,5-diphenylimidazole* (**9a**) and *2-butylamino-1-methyl-4,5-diphenylimidazole* (**9b**), respectively, were formed as the only products.

The products were isolated as hydrochlorides: a solution of crude **9a** and **9b**, respectively, was treated with 3 M HCl until pH 3–4 was obtained. After stirring for 1 h, the white precipitate was filtered, washed with diethyl ether, and dried. Yields of hydrochlorides: 80 and 70%, respectively. Then, a concentrated solution of ammonium hydroxide was added to a suspension of the hydrochloride in diethyl ether under vigorous stirring until pH 8–9 was reached. After 1 h at room temperature, the organic phase was separated and the aqueous phase was extracted with diethyl ether (3×). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated. Yields: 90% of **9a** and **9b**.

2-Methylamino-1-methyl-4,5-diphenylimidazole (9c). With methyl isothiocyanate (**8e**; 438.7 mg, 6 mmol). Colorless crystals with mp 231–233°C (methanol/acetone); yield: 600 mg (76%). IR: 3230*s*, 1615*vs*, 1600*vs*, 1590*s*, 705*vs*. ^{1}H NMR (DMSO-d_6): 7.54–7.09 (*m*, 10 arom. H); 3.42, 2.93 (2*s*, 2 CH_3N). ^{13}C NMR (DMSO-d_6): 150.7, 135.6, 131.8, 131.3, 123.9 (5*s*, C(2), C(4), C(5), 2 arom. C); 130.5, 128.8, 127.7, 125.7, 125.0, 123.7 (6*d*, 5 arom. CH); 29.6, 29.0 (2*q*, 2 CH_3N). CI-MS: 265 (18), 264 (100, $[M+1]^+$). Anal. Calcd for $C_{17}H_{17}N_3$ (263.34): C 77.54, H 6.51, N 15.96; found: C 77.44, H 6.36, N 15.96.

Reaction of 2-aminoimidazole 9d with phenyl isocyanate and phenyl isothiocyanate

A solution of 1 mmol of **9d** in 4 ml of dichloromethane was treated with 1.3 mmol of phenyl isocyanate. The solution was stirred at room temperature for 3 days. Evaporation of the solvent under vacuum afforded crude **10a** which was purified by recrystallization. Yield: 351 mg (79%).[¶]

The analogous reaction with phenyl isothiocyanate gave no thiourea derivative. More than 90% of **9d** were recovered unchanged.

Reactions of 1*H*-imidazole 3-oxides 5b–e with dimethyl acetylenedicarboxylate (DMAD)

General procedure: A solution of 284 mg (2 mmol) of DMAD in 4 ml of chloroform was cooled in a water/ice bath and stirred magnetically. Then, 2 mmol of respective **5** dissolved in 3 ml of chloroform were added in small portions in order to keep the temperature of the mixture at 0–5°C. When the addition was complete, the cooling bath was removed and the mixture was stirred at room temperature for 1 h. Evaporation of the solvent under vacuum afforded crude products **11** which were purified by recrystallization.

Dimethyl 3-(1-benzyl-2,3-dihydro-4,5-dimethyl-1*H*-imidazol-2-ylidene)-2-oxobutanedioate (11a). With **5b** (404.5 mg, 2 mmol). Colorless crystals; mp 200–202°C (diethyl ether/dichloromethane); yield: 410 mg (60%). IR: 2950*s*, 1720*vs* (C=O), 1670*vs* (C=O), 1650*vs* (C=O), 1560*vs*, 1540*s*, 1440*vs*, 1390*s*, 1310*vs*, 1240*vs*, 1220*vs*, 1200*vs*, 1140*s*, 1090*vs*, 1030*s*, 980*s*. ^{1}H NMR: 7.31–7.06 (*m*, 5 arom. H); 5.13 (*s*, CH_2N); 3.82, 3.52 (2*s*, 2 CH_3O); 2.17, 1.96 (2*s*, 2 CH_3). ^{13}C NMR: 208.7 (*s*, C=O ketone); 168.4, 167.8 (2*s*, 2 C=O ester); 143.7 (*s*, C(2)); 134.7 (*s*, 1 arom. C); 127.8, 127.2, 126.0 (3*d*, 5 arom. CH); 123.6, 123.2 (2*s*, C(4), C(5)); 80.9 (*s*, C=*C*); 52.2, 51.5 (2*q*, 2 CH_3O); 49.2 (*t*, CH_2N); 9.4, 8.9 (2*q*, 2 CH_3). CI-MS: 345 (70, $[M+1]^+$), 318 (16), 317 (100, $[(M+1)-CO]^+$), 314 (5), 313 (31), 285 (12, $[M-COOCH_3]^+$), 257 (5), 91 (14). Anal. Calcd for $C_{18}H_{20}N_2O_5$ (344.37): C 62.78, H 5.85, N 8.13; found: C 62.60, H 5.51, N 8.24.

Dimethyl 3-(1-cyclohexyl-2,3-dihydro-4,5-dimethyl-1*H*-imidazol-2-ylidene)-2-oxobutanedioate (11b). With **5c** (388.5 mg, 2 mmol). Colorless crystals; mp 206–208°C

[¶] Treatment of **9d** with cyclohexyl isocyanate under the same conditions yielded no urea derivative; **9d** was recovered in >90% yield.

(diethyl ether/dichloromethane); yield: 439 mg (64%). IR: 2950*vs*, 2870*s*, 1740*vs* (C═O), 1680*vs* (C═O), 1635*vs* (C═O), 1560*vs*, 1530*s*, 1450*vs*, 1370*s*, 1295*vs*, 1220*vs*, 1095*vs*, 1040*s*. ^{1}H NMR: 12.35 (*s*, NH); 4.15–4.10 (*m*, CHN); 3.83, 3.57 (2*s*, 2 CH_3O); 2.30, 2.13 (2*s*, 2 CH_3); 1.94–1.12 (*m*, 5 CH_2). ^{13}C NMR: 209.0 (*s*, C═O ketone); 169.4, 168.3 (2*s*, 2 C═O ester); 142.7 (*s*, C(2)); 124.8, 123.2 (2*s*, C(4), C(5)); 81.3 (*s*, C═*C*); 59.1 (*d*, CHN); 51.8, 50.6 (2*q*, 2 CH_3O); 31.1, 26.0, 25.3 (3*t*, 5 CH_2); 10.6, 9.1 (2*q*, 2 CH_3). EI-MS: 337 (5, $[M+1]^+$), 336 (12, $M^{+\cdot}$), 278 (15), 277 (100, $[M-COOCH_3]^+$), 249 (5), 195 (36), 194 (13), 167 (12), 136 (11), 135 (37), 83 (13). Anal. Calcd for $C_{17}H_{24}N_2O_5$ (336.39): C 60.70, H 7.19, N 8.33; found: C 60.14, H 7.12, N 7.97.

Dimethyl 3-(1-cyclohexyl-2,3-dihydro-4,5-diphenyl-1*H*-imidazol-2-ylidene)-2-oxobutanedioate (11c). With **5d** (636.8 mg, 2 mmol). Colorless crystals; mp 219–221°C (methanol); yield: 760 mg (83%). IR: 2940*vs*, 2855*s*, 1720*vs* (C═O), 1680*vs* (C═O), 1635*vs* (C═O), 1560*vs*, 1540*s*, 1430*vs*, 1390*s*, 1370*s*, 1300*s*, 1230*s*, 1160*s*, 1100*s*, 1070*vs*, 1000*s*, 780*vs*. ^{1}H NMR: 7.49–7.01 (*m*, 10 arom. H); 4.06–4.02 (*m*, CHN); 3.79, 3.68 (2*s*, 2 CH_3O); 1.89–1.47, 1.19–0.80 (2*m*, 5 CH_2). ^{13}C NMR: 202.5 (*s*, C═O ketone); 168.4, 167.9 (2*s*, 2 C═O ester); 144.4 (*s*, C(2)); 132.1, 130.1, 127.7, 127.3 (4*s*, 2 arom. C, C(4), C(5)); 128.8, 128.7, 128.2, 126.8 (4*d*, 10 arom. CH); 82.0 (*s*, C═*C*); 60.6 (*d*, CHN); 51.8, 50.9 (2*q*, 2 CH_3O); 32.0, 26.2, 24.9 (3*t*, 5 CH_2). EI-MS: 461 (19, $[M+1]^+$), 460 (69, $M^{+\cdot}$), 402 (19), 401 (77, $[M-COOCH_3]^+$), 400 (28), 373 (23), 319 (80), 317 (100), 292 (21), 291 (55), 260 (28), 259 (70), 233 (10), 193 (18), 165 (11), 128 (12), 103 (15). Anal. Calcd for $C_{27}H_{28}N_2O_5$ (460.53): C 70.42, H 6.13, N 6.08; found: C 70.36, H 6.07, N 6.20.

Dimethyl 3-(2,3-dihydro-1,4,5-trimethyl-1*H*-imidazol-2-ylidene)-2-oxobutanedioate (11d). With 1,4,5-trimethyl-1*H*-imidazole 3-oxide (**5d**; 252.32 mg, 2 mmol). Colorless crystals; mp 189–191°C (diethyl ether/dichloromethane); yield: 320 mg (60%). IR: 2955*m*, 1730*vs* (C═O), 1650*vs* (C═O), 1510*vs*, 1445*s*, 1305*m*, 1200*s*, 1070*s*. ^{1}H NMR: 11.19 (*s*, NH); 3.84, 3.63 (2*s*, 2 CH_3O); 3.44 (*s*, CH_3N); 2.19, 2.16 (2*s*, 2 CH_3). ^{13}C NMR: 208.6 (*s*, C═O ketone); 168.8, 167.3 (2*s*, 2 C═O ester); 143.5 (*s*, C(2)); 123.1, 121.9 (2*s*, C(4), C(5)); 81.2 (*s*, C═*C*); 51.7, 50.9 (2*q*, 2 CH_3O); 32.7 (*q*, CH_3N); 9.0, 8.4 (2*q*, 2 CH_3). CI-MS: 269 (100, $[M+1]^+$), 209 (21). Anal. Calcd for $C_{12}H_{16}N_2O_5$ (268.27): C 53.73, H 6.01, N 10.44; found: C 53.72, H 5.83, N 10.09.

Crystal structure determination of 9c

(See Fig. 1.[18]) The intensities were collected on a Rigaku AFC5R diffractometer using graphite-monochromated MoK_α radiation and a 12 kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. The structure was solved by direct methods using SHELXS86,[19] which revealed the positions of all non-H atoms. The non-H atoms were refined anisotropically. All of the H-atoms were located in a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. Refinement of the structure was carried out on F using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o|-|F_c|)$.[2] A correction for secondary extinction was not applied. Neutral atom scattering factors for non-H atoms were taken from Ref. 20, and the scattering factors for H-atoms from Ref. 21. Anomalous dispersion effects were included in F_{calc};[22] the values for f' and f'' were those of Ref. 23. All calculations were performed using the TEXSAN crystallographic software package.[24]

Crystal data for 9c

A crystal of dimension 0.15×0.25×0.45 mm^3 was grown from methanol. $C_{17}H_{17}N_3$, M_r=263.34, orthorhombic, space group *Pbca*, a=12.485(2), b=26.134(3), c=8.580(2) Å, V=2799.3(9) Å^3, Z=8, D_c=1.250 g cm^{-3}, μ(MoK_α)=0.0757 mm^{-1}; T=173(1) K, λ=0.71069 Å. Cell dimension from 25 reflections in the range 2θ=26–37°, ω scans, $2\theta_{(max)}$=55°, 4286 reflections measured, 3219 symmetry-independent reflections, 2183 reflections with $I>2\sigma(I)$ used in the refinement of 249 parameters. Final R=0.0393, wR=0.0346 ($w=[\sigma^2(F_o)+(0.005F_o)^2]^{-1}$), GoF=1.527, Δ_{max}/σ=0.0004, $\Delta\rho$(max; min)=0.19; −0.18 e Å^{-3}.

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