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A Domino Annulation Reaction under Willgerodt−Kindler Conditions

Daniel Kadzimirsz,[†] Daniel Kramer,[†] Lertnarong Sripanom,[†] Iris M. Oppel,[†] Pawel Rodziewicz,[‡] Nikos L. Doltsinis,[‡,§] and Gerald Dyker*,[†]

Faculty of Chemistry & Biochemistry, Ruhr-Universität Bochum, Universitätsstrasse 150, D-44780 Bochum, Germany, Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum, D-44780 Bochum, Germany, and Department of Physics, King's College London, Strand, London WC2R 2LS, United Kingdom

gerald.dyker@ruhr-uni-bochum.de

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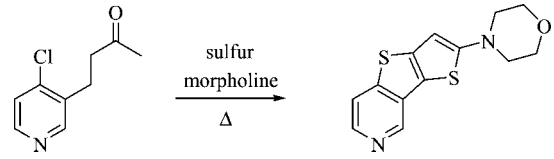
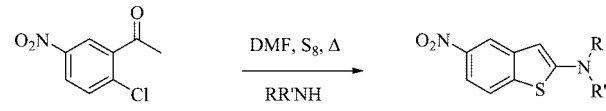


Butanone side chains at arenes and hetarenes, efficiently introduced by a Heck-type reaction, are transformed to annulated thieno[3,2-*b*]thiophenes in a domino redox process under Willgerodt−Kindler conditions. A nucleophilic aromatic substitution with an intermediary thioenolate is a reasonable key step of this process.

Introduction

One can hardly imagine an experiment which appears more alchemy-like than a Willgerodt−Kindler reaction:[1] elemental sulfur is directly applied as reagent, developing hydrogen sulfide while being heated up in a mixture with the substrate and an additional amine. On the other hand, the underlying mechanism is far from being completely understood, certainly representing an extremely complex redox cascade. Presumably, both radicals and anionic nucleophiles have to be discussed as reactive intermediates. We became interested in studying domino processes under Willgerodt−Kindler conditions as powerful methods for CH transformation.[2,3] Recently, Neckers et al.[4] reported a new entry to functionalized benzothiophenes **2** (Scheme 1), which profits from the easy access to the acetyl-substituted substrates **1**. Obviously, the acetyl group undergoes several redox steps, finally ending up as C_2-unit within the thiophene moiety after an intramolecular nucleophilic aromatic substitution with an intermediary thiolate as key step.

SCHEME 1. Monoannulation Reaction under Willgerodt−Kindler Conditions According to Neckers et al[3]



1 R = H, R' = allyl: 45%; R-R' = $(CH_2)_2O$: 12% **2**

We wish to report on a related domino annulation reaction, which oxidatively transforms up to six CH bonds, giving rise to tri- and tetracyclic ring systems with a thieno[3,2-*b*]thiophene moiety.[5] This process is both of mechanistic interest and of preparative importance since the resulting highly functionalized polyheterocyclic systems with flat and at the same time slightly curved topology can be regarded as potential DNA intercalators.[6]

Results and Discussion

The butanone chain of our model compounds is readily introduced in good to excellent yields by a Heck-type reaction of aryl iodides **3** with allylic alcohol **4** (Scheme 2),[7] providing

[†] Faculty of Chemistry & Biochemistry, Ruhr-Universität Bochum.
[‡] Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum.
[§] King's College London.

(1) (a) Willgerodt, C. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 534–536. (b) Kindler, K. *Liebigs Ann. Chem* **1923**, *431*, 187–207.
(2) *Handbook of C−H Transfomations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, Germany, 2005.
(3) Dyker, G.; Kadzimirsz, D. *Eur. J. Org. Chem.* **2003**, 3167–3172.
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(6) (a) Audoux, J.; Achelle, S.; Turck, A.; Marsais, F.; Ple, N. *J. Heterocycl. Chem.* **2006**, *43*, 1497–1503. (b) Xu, Y.; Qu, B.; Qian, X.; Li, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1139–1142.
(7) (a) Dyker, G.; Thöne, A. *J. Prakt. Chem.* **1999**, *341*, 138–141. (b) Dyker, G.; Grundt, P.; Markwitz, H.; Henkel, G. *J. Org. Chem.* **1998**, *63*, 6043–6047, and references cited therein.

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SCHEME 2. Heck-Type Synthesis of 2-Arylbutanones 5[a]

3	**4** (3 equiv.)	**5**
3a: 1-chloro-2-iodobenzene		**5a** (95%)
3b: 4-chloro-3-iodobenzonitrile		**5b** (76%)
3c: 4-chloro-3-iodopyridine		**5c** (65%)
3d: 4-methoxy-3-iodopyridine		**5d** (65%)
3e: 4-chloro-3-iodo-2-methylquinoline		**5e** (85%)
3f: 1-chloro-2-iodo-5-nitrobenzene		**5f** (89%)
3g: 1-chloro-2-iodo-4-nitrobenzene		**5g** (87%)

[a] Conditions: (a) 5% $Pd(OAc)_2$, LiCl, Et_3N, DMF, 3 days at 120 °C.

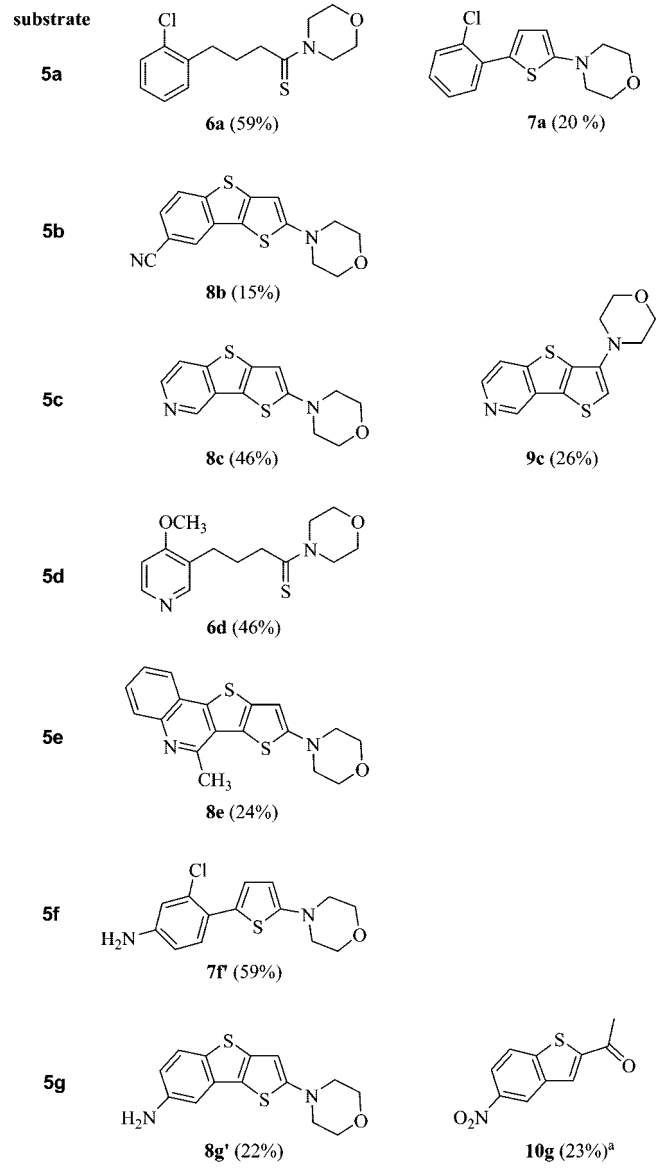
a C_4-unit for the Willgerodt−Kindler redox process. In this process, the Pd catalyst selectively reacts with the iodoarenes in the presence of chloro substituents. Obviously, also nitro groups are tolerated.

In our first attempt for a Willgerodt−Kindler reaction with an arylbutanone **5**, the aryl group remained unaffected; as anticipated, the 2-chlorophenyl group of **5a** was inert toward nucleophilic aromatic substitution even under the relatively harsh reaction conditions A (morpholine, sulfur, 6 h at 130 °C without additional solvent). However, two products were isolated in satisfactory yield: the thioamide **6a** as ordinary Willgerodt−Kindler product, and the aminothiophene **7a**, a type of product frequently observed earlier (Scheme 3).[8] An additional cyano group in the *para*-position obviously sufficiently activates: Willgerodt−Kindler conditions transform benzonitrile **5b** to a rather complex product mixture, from which we were able to isolate the highly functionalized thieno[3,2-*b*]benzothiophene **8b** as a tricyclic ring system, resulting from a domino annulation process. Therefore, we tested related model compounds with acceptor-substituted aryl chlorides, hoping that this process is generally applicable. The 4-chloropyridine moiety of **5c** is also electrophilic enough for intramolecularly intercepting thiolate intermediates of the Willgerodt−Kindler reaction, thus leading to the isomeric tricyclic arenes **8c** and **9c** in rather good yields. Both spectroscopically characterized regioisomers were distinguished by NMR spectroscopy: in the HMBC spectrum of the major regioisomer, the thiophenyl hydrogen is correlated with two quaternary carbons via two bonds (^2J-correlation) and with a third quaternary carbon via three bonds (^3J-correlation), being in accord with structure **8c**. Moreover, for this isomer, a signal at 162.9 ppm is registered in the ^{13}C NMR spectrum, typical for the N,S-acetal moiety. Regioisomers analogous to **9c** were also detected in the ^1H NMR spectra of the crude products of the reactions with substrates **5b** and **5e** but could not be isolated as pure samples.

In contrast to a chloride group, the methoxy group of substrate **5d** is inert under the reaction conditions. Therefore, no annulation reaction takes place and the usual thioamide **6d** is the result. Consequently, we concentrated on other aryl chlorides for our test reactions. As anticipated, 4-chloroquinoline **5e** was transformed to the tetracyclic annulation product **8e**, which could be of interest as a potential DNA intercalator.[6]

We succeeded in growing single crystals of the monohydrate of **8e**. According to the X-ray crystal analysis, the tetracyclic hetarenes are stacked at a separation of 3.572(5) Å and, in addition, cramped by hydrogen bonds to the crystal water molecules. While

SCHEME 3. Products from the Transformation of 2-Arylbutanones 5 under Willgerodt−Kindler Reaction Conditions[a]



[a] Morpholine, sulfur, 6 h at 130 °C (see Experimental Section: conditions A, reducing nitro groups!); a: moderate reaction conditions; morpholine, sulfur, diluted with DMF, shorter reaction time, 12 min at 100 °C (see Experimental Section: conditions B).

one hydrogen bond might be regarded as ordinary linear— also typical for pyridine water complexes[10]— the other one is somewhat unusual: the OH bond points perpendicularly toward the sp^2-hybrid orbital of the free electron pair of the next quinoline nitrogen. According to DFT calculations of the infinite periodic crystal, this arrangement represents at least a local energy minimum, which allows two positively polarized hydrogen atoms to simultaneously coordinate to one free electron pair; with fixed positions of the hetarene atoms, the position of the water molecule does not change

(8) (a) Asinger, F.; Saus, A.; Mayer, A. *Monatsh. Chem.* **1967**, *98*, 825–836. (b) Xu, Y.; Qu, B.; Qian, X.; Li, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1139–1142.

(9) X-ray crystal structure analysis of **8e**: Pale orange prism, 0.32 × 0.28 × 0.23 mm^3, monoclinic, $P2_1/n$, a = 17.056(2), b = 3.9938(5), c = 23.829(3) Å, β = 98.49(1)°, V = 1605.4(3) Å^3, ρ_{calc} = 1.483 gcm^{-3}, $2\theta_{max}$ = 50.50°, λ = 0.71073 Å, T = 113 K, 8141 measured reflections, 2892 independent reflections (R_{int} = 0.0368), 2084 observed reflections ($I > 2\sigma(I)$), μ = 0.345 mm^{-1}, 224 parameters, R_1 ($I > 2\sigma(I)$) = 0.0354, wR_2 (all data) = 0.0846, max/min residual electron density 0.301/−0.287 eÅ^{-3}.

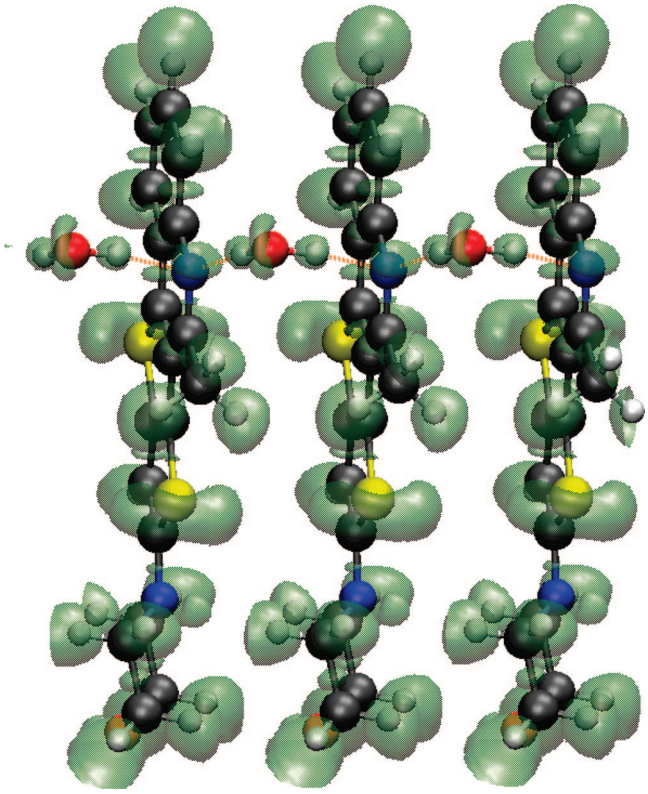


FIGURE 1. Structure of the monohydrate of **8e** in the crystal[9] and calculated electron localization function (ELF). Shown are three periodic layers of the tetracyclic hetarene bridged by a water molecule whose position and structure are detailed in Table 1. For further details concerning the electronic structure, see the text.

qualitatively during geometry optimization. Figure 1 illustrates the electronic structure of the crystal in terms of the electron localization function (ELF). Focusing on the water molecule bridging the two nitrogen hetarene atoms, we can clearly see the two lone pairs on the water oxygen and the rather diffuse lone pair on nitrogen. In addition, on each of the water hydrogen atoms, there is a basin of attraction whose shape is typical of hydrogen bonds. The nitrogen lone pair is seen to lean toward the closer water hydrogen (at a calculated distance of $R(N\cdots H_l) = 1.70$ Å; for details about the notation, see Table 1). The corresponding hydrogen bond angle $O-H_l-N$ is 173.4°, further underlining the strength of this nearly linear H bond. As a measure for the orientation of the H bond with respect to the hetarene layer, we use the $C-N-H_l$ angle between the carbon atom opposite the nitrogen in the six-membered ring, the nitrogen atom, and the left (in Figure 1) water hydrogen atom. The value of 159.3° indicates that this stronger hydrogen bond essentially lies in the plane of the hetarene molecule. The other hydrogen bond is somewhat longer (the calculated distance is $R(N\cdots H_r) = 1.80$ Å). It is somewhat further from linearity having a $O-H_r-N$ angle of 162.9° and is oriented nearly perpendicular to the hetarene layer at a $C-N-H_r$ angle of 113.2°, explaining its weakness relative to the first H bond. The geometrical data describing the bridging water molecule shown in Figure 1 are summarized in Table 1.

With a nitro group in the *meta*-position to the chloride, such as in substrate **5f**, the nucleophilic aromatic substitution is of course not favored; however, instead of the usually major

TABLE 1. Bond Lengths and Angles Characterizing the Bridging Water Molecule between the Nitrogen Atoms of the Two Tetracyclic Hetarene Layers[a]

distance (Å)	
$R(N\cdots H_r)$	1.797
$R(OH_r)$	0.980
$R(O\cdots N)$	2.749
$R(N\cdots H_l)$	1.703
$R(OH_l)$	1.000
$R(O\cdots N)$	2.699
angle (deg)	
$O-H_r-N$	162.87
$O-H_l-N$	173.44
H_r-O-H_l	106.45
$C-N-H_l$	159.34
$C-N-H_r$	113.15

[a] O refers to the oxygen atom of the H_2O molecule, H_l and H_r are its left and right (in the orientation shown in Figure 1) hydrogen atoms, N is the hetarene nitrogen site bridged by the H_2O molecule, and C is the carbon atom which lies opposite to N in the hetarene six-membered ring.

thioamide, we obtained a good yield of the morpholino thiophene **7f′** in this case. Simultaneously, the nitro group is reduced, resulting in the aniline function of **7f′** and demonstrating that Willgerodt−Kindler conditions are both oxidative and reductive. With the activating *para*-nitro group of **5g**, the synthesis of the corresponding tricyclic hetarene **8g′** is successful, despite the reduction of the nitro group, which must have taken place after the nucleophilic cyclization. Indeed, under moderate reaction conditions (diluted with DMF as solvent and just 100 °C for 12 min), we were able to isolate the monocyclization product **10g** with an intact[11] nitro group. According to orientating experiments, this type of acetyl benzothiophenes can indeed be oxidatively cyclized under the rather harsh reaction conditions A. Therefore, we regard **10g** as an intermediary product on the way to tricycle **8g′**.

Our general mechanistic rationale[12] is depicted in Scheme 4: a suitable leaving group X and an activating, electron-withdrawing functional group G are prerequisite for the domino annulation process to take place. The first sulfur atom is oxidatively introduced, presumably via intermediary enamines, to give thioketones **12**, whose corresponding thioenolate is prone to cyclize by nucleophilic aromatic substitution, thus giving rise to acetyl benzothiophenes **13** (or the corresponding enamine) and explaining the isolation of **10g** as result under moderate reaction conditions. Subsequent studies should test the reactivity of acetyl benzothiophenes **13** under forcing Willgerodt−Kindler conditions in detail, trying to verify the transformation to **14** via thiols **15** and **16** on a preparative scale, while we could already prove the validity of this working hypothesis by an orientating small scale test with the parent acetyl benzothiophene.

In conclusion, we have developed a domino process under Willgerodt−Kindler conditions, which transforms a simple butanone side chain of suitable functionalized arenes and

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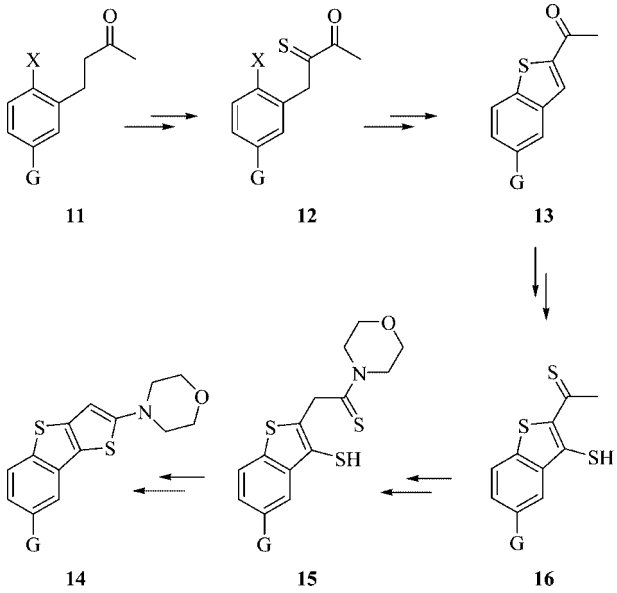
SCHEME 4. Mechanistic Rationale for the Domino Annulation Process (Intermediary Enamines Are Omitted)[a]



[a] X = leaving group, G = functional group activating for nucleophilic aromatic substitution.

hetarenes into at least tricyclic annulated thieno[3,2-*b*]-thiophenes. Mechanistic considerations allow one to identify other types of substrates as promising candidates for oxidative heteroannulation reactions, which are currently under investigation.

Experimental Section

General Remarks: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded by use of $CDCl_3$ as solvent and TMS as the internal standard. Procedures for the synthesis of arylbutanones **5** by Heck reaction are provided in the Supporting Information.

Willgerodt−Kindler Reaction with 4-Arylbutan-2-ones (5), General Procedures. Method A. A mixture of 1.0−1.5 mmol of the 4-arylbutan-2-one (**5**; see Supporting Information), 10 mL of morpholine, and 190 mg (6.0 mmol) of sulfur in a screw-capped tube was heated under stirring for 6 h at 130 °C. The excess morpholine was removed in vacuo in the Kugelrohr oven, and the residue was solubilized in 10 mL of methyl *tert*-butyl ether to be filtered through a small pad of silica (3 g). After concentrating in vacuo at the rotatory evaporator, the residue was fractionated by flash chromatography. This method usually produces various amounts of 1-morpholin-4-ylethanthione[13] (and related compounds such as 1,2-dimorpholin-4-ylethane-1,2-dithione[14]) as solid yellow to orange byproduct: ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.67 ppm (s, 3H, *H-2*), 3.75−3.81 (m, 6H), 3.80 (t, J = 5.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 32.1 ppm (q), 49.6 (t), 50.2 (t), 66.2 (t), 66.4 (t), 199.0 (s). **Method B:** A mixture of 1.0 mmol of 4-arylbutan-2-one (**5**), 10 mL of morpholine, 5 mL of DMF, and 190 mg (6.0 mmol) of sulfur was heated under argon for 12 min at 130 °C. The excess morpholine, as well as the solvent DMF, was removed in vacuo in the Kugelrohr oven. The residue was solubilized in 10 mL of methyl *tert*-butyl ether to be filtered through a small pad of silica (3 g). After concentrating in vacuo at the rotatory evaporator, the residue was fractionated by flash chromatography.

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Willgerodt−Kindler Reaction with 4-(2-Chlorophenyl)butan-2-one (5a). A quantity of 274 mg (1.5 mmol) of butanone **5a** was transformed according to the general procedure (Method A). The crude product was fractionated by flash chromatography (silica, methyl *tert*-butyl ether/petrol ether 1:8): **1st Fraction** (R_f = 0.56): 83 mg (20 %) of *N*-[5-(2-chlorophenyl)thiophen-2-yl]morpholine (**7a**) as colorless oil: IR (KBr) $\tilde{\nu}$ = 2964 cm^{-1} (m), 2864 (m), 1546 (w), 1492 (s), 1447 (m), 1377 (m), 1264 (m), 1220 (m), 1214 (m), 1032 (m), 895 (m), 756 (s), 617 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.18 ppm (m, 4H), 3.85 (m, 4H), 6.13 (d, J = 4.0 Hz, 1H), 7.13 (d, J = 4.0 Hz, 1H), 7.14 (m, 1H), 7.23 (m, 1H), 7.41 (dd, J = 8.0, 1.5 Hz, 1H), 7.46 (dd, J = 7.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 51.2 ppm (t), 66.4 (t), 105.2 (d), 126.4 (s), 126.9 (d), 127.1 (d), 127.5 (d), 130.5 (d), 130.6 (d), 131.6 (s), 133.4 (s), 159.8 (s); MS (EI, 70 eV) *m*/*z* (%) = 279 (100) [M$^+$], 221 (36), 192 (3), 186 (17), 149 (10), 86 (24); HRMS calcd for $C_{14}H_{14}NOSCl$ 279.04845 g/mol), found 279.01912 g/mol. **2nd Fraction** (R_f = 0.35): 248 mg (59 %) of *N*-(4-(2-chlorophenylthiobutyl)morpholine (**6a**) as colorless oil; IR (KBr) $\tilde{\nu}$ = 2968 cm^{-1} (m), 2860 (m), 1471 (s), 1443 (m), 1281 (s), 1254 (m), 1226 (m), 1115 (s), 1022 (m), 882 (m), 764 (s), 676 (m); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.92−2.12 ppm (m, 2H), 2.80−2.94 (m, 4H), 3.61−3.71 (m, 4H), 3.74−3.79 (m, 2H), 4.33 (t, J = 4.9 Hz, 2H), 7.10−7.22 (m, 3H), 7.28−7.39 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 28.9 ppm (t), 32.9 (t), 49.8 (t), 49.9 (t), 66.4 (2t), 126.9 (d), 127.6 (d), 129.5 (d), 130.5 (d), 133.7 (s), 138.7 (s), 203.0 (s); MS (EI, 70 eV) *m*/*z* (%) = 283 (22) [M$^+$], 248 (100), 158 (11), 145 (56), 125 (11), 112 (35), 86 (50), 43 (42); HRMS calcd for $C_{14}H_{18}NOSCl$ 283.07976 g/mol, found 283.08055 g/mol.

Willgerodt−Kindler Reaction with 4-Chloro-3-(3-oxobutyl)-benzonitrile (5b). A quantity of 207 mg (1.00 mmol) of butanone **5b** was transformed according to the general procedure (Method A, 14 h reaction time at 130 °C). The crude product was fractionated by gradient chromatography (silica, petrol ether/methyl *tert*-butyl ether in the ratios of 95:5, 90:10, 80:20, 50:50, 20:80, and 0:100). The 90:10 fraction was concentrated, further purified by flash chromatography (silica, petrol ether/ethyl acetate 5:1, R_f = 0.16), and recrystallized (from dichloromethane/pentane 1:3) to give 45 mg (15%) of 2-morpholin-4-ylthieno[3,2-*b*][1]benzothiophene-7-carbonitrile (**8b**) as yellow crystals with mp 205 °C: IR (KBr) $\tilde{\nu}$ = 2928 cm^{-1} (w), 2216 (m), 1521 (s), 1473 (m), 1444 (m), 1381 (w), 1267 (w), 1221 (w), 1113 (m), 924 (w); UV/vis (dichloromethane) λ_{max} (log ε) = 217 nm (3.43), 232 (3.85), 281 (4.11), 288 (4.12), 333 (4.09); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.25 ppm (t, J = 4.8 Hz, 4H), 3.89 (t, J = 4.8 Hz, 4H), 6.34 (s, 1H), 7.42 (dd, J = 8.3, 1.5 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 50.7 ppm (t), 66.0 (t), 97.3 (s), 108.03 (s), 119.3 (s), 120.6 (d), 122.7 (d), 124.0 (d), 124.5 (d), 133.5 (s), 139.4 (s), 144.4 (s), 162.9 (s); MS (EI, 70 eV) *m*/*z* (%) = 301 (19), 300 (100) [M$^+$], 258 (29), 243 (22), 242 (43), 228 (9), 215 (20), 202 (6), 170 (14), 121 (12); HRMS calcd for $C_{15}H_{12}N_2OS_2$ 300.03909, found 300.03955.

Willgerodt−Kindler Reaction with 4-[4-Chloropyridin-3-yl]butan-2-one (5c). A quantity of 275 mg (1.5 mmol) of pyridine derivative **5c** was transformed according to the general procedure (Method A, 6 h at 130° C). The crude product was fractionated by flash chromatography (silica, methyl *tert*-butyl ether). **1st Fraction** (R_f = 0.31): 92 mg (26 %) of 1-morpholin-4-yl-3,8-dithia-5-azacyclopenta[*a*]indane (**9c**) as a yellow solid with mp 144° C; IR (KBr) $\tilde{\nu}$ = 3112 cm^{-1} (w), 2927 (s), 2843 (m), 1518 (s), 1451 (m), 1383 (m), 1265 (m), 1117 (s), 814 (w), 717 (m), 675 (w); UV (acetonitrile) λ_{max} (log ε) = 347 nm (3.64, br), 307 (4.01), 304 (4.01), 300 (4.01); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.22 ppm (t, J = 4.5 Hz, 4H), 3.92 (t, J = 4.5 Hz, 4H), 6.54 (s, 1H, *H-2*), 7.78 (d, J = 5.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 9.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 50.8 ppm (t), 66.7 (t), 106.0 (d), 118.5 (d), 129.5 (s), 131.2 (s), 132.3 (s), 142.7 (d), 143.3 (d), 145.4 (s), 149.9 (s); MS (EI, 70 eV) *m*/*z* (%) = 276 (100) [M$^+$], 261 (9), 218 (74), 204 (7), 191 (23), 149 (28), 109 (14), 57 (36); HRMS

calcd for $C_{13}H_{12}N_2OS_2$ 276.03894 g/mol, found 276.03948 g/mol. **2nd Fraction** (R_f = 0.22): 163 mg (46 %) of 2-morpholin-4-yl-3,8-dithia-5-azacyclopenta[*a*]indane (**8c**) as yellow solid with mp 182 °C; IR (KBr) $\tilde{\nu}$ = 3112 cm^{-1} (w), 2927 (s), 2843 (m), 1518 (s), 1451 (m), 1383 (m), 1265 (m), 1117 (s), 814 (w), 717 (m), 675 (w); UV (acetonitrile) λ_{max} (log ε) = 358 nm (4.21, br), 306 (4.46), 301 (4.45), 299 (4.34), 296 (4.45); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.24 ppm (t, J = 4.8 Hz, 4H), 3.88 (t, J = 4.8 Hz, 4H), 6.36 (s, 1H), 7.71 (d, J = 5.5 Hz, 1H), 8.36 (d, J = 5.5 Hz, 1H), 8.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 51.1 ppm (t), 66.2 (t), 97.7 (d), 118.3 (d), 119.5 (s), 130.2 (s), 138.1 (s), 141.0 (d), 141.6 (d), 148.2 (s), 162.9 (s); MS (EI, 70 eV) *m*/*z* (%) = 276 (100) [M$^+$], 260 (20), 218 (50), 204 (11), 86 (42); HRMS calcd for $C_{13}H_{12}N_2OS_2$ 276.03894 g/mol, found 276.03948 g/mol.

Willgerodt−Kindler Reaction with 4-[4-Methoxypyridin-3-yl]butan-2-one (5d). A quantity of 270 mg (1.5 mmol) of butanone **5d** was transformed according to the general procedure (Method A). The crude product was purified by flash chromatography (silica, ethyl acetate/triethylamine 97:3, R_f = 0.35): 193 mg (46%) of *N*-(4-(4-methoxy-pyridin-3-yl)thiobutyl)morpholine (**6d**) as slightly yellow oil; IR (KBr) $\tilde{\nu}$ = 2975 cm^{-1} (m), 2927 (m), 2862 (m), 1586 (s), 1488 (s), 1448 (m), 1284 (s), 1237 (m), 1192 (m), 1114 (s), 1021 (s), 829 (m), 782 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.97−2.05 ppm (m, 2H), 2.70 (t, J = 7.6 Hz, 2H), 2.86 (m, 2H), 3.64−3.71 (m, 4H), 3.76 (m, 2H), 3.87 (s, 3H), 4.33 (t, J = 5.0 Hz, 2H), 6.77 (d, J = 5.5 Hz, 1H), 8.25 (s, 1H), 8.37 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.2 ppm (t), 28.6 (t), 42.8 (t), 49.9 (t), 50.0 (t), 55.2 (q), 66.4 (t), 66.5 (t), 105.9 (d), 125.3 (s), 149.7 (d), 150.3 (d), 163.8 (s), 203.3 (s); MS (EI, 70 eV) *m*/*z* (%) = 280 (23) [M$^+$], 265 (3), 238 (3), 136 (100), 86 (15), 43 (16); HRMS calcd for $C_{14}H_{20}N_2O_2S$ 280.12455 g/mol, found 280.12505 g/mol.

Willgerodt−Kindler Reaction with 4-(4-Chloro-2-methylquinolin-3-yl)butan-2-one (5e). A quantity of 250 mg (1.00 mmol) of butanone **5e** was transformed according to the general procedure (Method A). The crude product was purified by gradient chromatography (silica, dichloromethane/methyl *tert*-butyl ether in the ratios of 100:0, 90:10, 80:20, 50:50, 20:80, 0:100; TLC: silica, methyl *tert*-butyl ether, R_f = 0.23): 84 mg (24%) of 10-methyl-2-*N*-morpholinothieno[2′,3′:4,5]thieno[2,3-*c*]quinoline hydrate (**8e**) as a yellow solid with mp 201 °C; IR (KBr) $\tilde{\nu}$ = 2964 cm^{-1} (w), 2877 (w), 1726 (m), 1523 (s), 1440 (s), 1381 (w), 1262 (m), 1155 (m), 1119 (m), 1036 (w), 869 (m), 761 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.93 ppm (s, 3H), 3.25 (t, J = 6.0 Hz, 4H), 3.85 (t, J = 6.0 Hz, 4H), 6.41 (s, 1H), 7.51 (t, J = 7 Hz, 1H), 7.61 (t, J = 7 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.5 (s), 49.5 (d), 64.5 (d), 96.5 (t), 120.6 (q), 120.7 (q), 122.5 (t), 124.6 (t), 125.8 (q), 126.0 (t), 127.7 (t), 135.3 (q), 141.5 (q), 142.9 (q), 150.0 (q), 161.0 (q); MS (FAB) *m*/*z* (%) 340.069 (100) [M$^+$]. Anal. Calcd for $C_{18}H_{16}N_2OS_2$ (340.46) +1.5 H_2O: C, 58.83; H, 5.21; N, 7.62. Found: C, 58.89; H, 4.89; N, 7.81. HRMS calcd for $C_{18}H_{16}N_2OS_2$: 340.0704 g/mol, found 340.0696 g/mol.

Willgerodt−Kindler Reaction with 4-[2-Chloro-4-nitrophen-3-yl]butan-2-one (5f). A quantity of 270 mg (1.5 mmol) of butanone **5f** was transformed according to the general procedure (Method A). The crude product was purified by flash chromatography with all fractions kept under argon (silica, methyl *tert*-butyl ether/petrol ether 1:8, R_f = 0.20): 261 mg (59%) of *N*-(5-(2-chloro-4-aminophenyl)thiophen-2-yl)morpholine (**7f′**) as slightly yellow oil; IR (KBr) $\tilde{\nu}$ = 3364 cm^{-1} (m), 2966 (m), 2859 (m), 1621 (s), 1557 (m), 1504 (s), 1451 (m), 1298 (s), 1258 (m), 1201 (m), 1117 (m), 903 (m), 859 (m), 817 (m), 729 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.11 ppm (t, J = 5.8 Hz, 4H), 3.85 (t, J = 5.8 Hz, 4H), 3.86 (s, br, 2H), 6.19 (d, J = 1.5 Hz, 1H), 6.56 (dd, J = 8.3 Hz, 2.5, 1H), 6.76 (d, J = 2.5 Hz, 1H), 7.02 (d, J = 1.5 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 50.7 ppm (t), 66.7 (t), 100.5 (d), 113.6 (d), 116.1 (d), 119.5 (d), 123.4 (s), 132.0 (d), 133.0 (s), 140.5 (s), 147.0 (s), 151.7 (s, *C-2*); MS (EI, 70 eV) *m*/*z* (%) = 294 (100) [M$^+$], 279 (10), 236 (67), 164 (13). Anal. Calcd for $C_{14}H_{15}ClN_2OS$ (294.80) +1 H_2O: C, 53.76; H, 5.48; N, 8.96. Found: C, 54.42; H, 5.06; N, 8.72 (a slight deviation because the water content of this sensitive hygroscopic oil is not exactly 1 equiv).

Willgerodt−Kindler Reaction with 4-(2-Chloro-5-nitrophenyl)butan-2-one (5g). A quantity of 227 mg (1.00 mmol) of butanone **5g** was transformed according to the general procedure (Method A, 6 h reaction time at 130 °C). The crude product was fractionated by gradient chromatography (silica, dichloromethane/methyl *tert*-butyl ether in the ratios of 100:0, 90:10, 80:20, 50:50, 20:80, 0:100, 100 mL of each). The 90:10 fraction was purified once again by flash chromatography (TLC: silica, petrol ether/methyl *tert*-butyl ether, 1:1; R_f = 0.11). After evaporation of the solvent, the residue was recrystallized twice (from dichloromethane/pentane 1:3) to give 63 mg (22%) of 7-amino-2-(morpholin-4-yl)thieno[3,2-*b*][1]benzothiophene (**8g′**) as yellow crystals with mp 205 °C: IR (KBr) $\tilde{\nu}$ = 3418 cm^{-1} (s), 3354(s), 2826 (m), 1617 (w), 1593 (m), 1523 (s), 1485 (w), 1444 (w), 1428 (m), 1215 (w), 1116 (m); UV/vis (dichloromethane) λ_{max} (log ε) = 215 nm (3.59), 232 (3.96), 259 (4.09), 327 (4.15); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ = 1.53 ppm (s, 2H), 3.18 (t, J = 4.9 Hz, 4H), 3.85 (t, J = 4.9 Hz, 4H), 6.29 (s, 1H), 6.62 (dd, J = 8.6, 2.3 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H); MS (EI, 70 eV) *m*/*z* (%) = 290 (100) [M$^+$], 232 (27), 205 (11), 116 (12); HRMS calcd for $C_{14}H_{14}N_2OS_2$ 290.0547, found 290.05515. **Alternative Method B:** A quantity of 227 mg (1.00 mmol) of butanone **5g** was transformed according to the general procedure (Method B, 12 min reaction time at 100 °C). The crude product was fractionated by flash chromatography (silica, petrol ether/methyl *tert*-butyl ether, 1:1; R_f = 0.35, 0.10 (1-morpholinoethanethione[13]). The fraction with R_f = 0.35 was isolated: 50 mg (23%) of 1-(5-nitrobenzo[*b*-]thiophen-2-yl)ethanone (**10g**) as yellow crystals with mp 175−177 °C; IR (KBr) $\tilde{\nu}$ = 3100 cm^{-1} (w), 1669 (s), 1523 (w), 1505 (m), 1340 (s), 1270 (w), 825 (w), 742 (w); UV/vis (dichloromethane): λ_{max} (log ε) = 218 nm (3.10), 222 (3.12), 225 (3.12), 280 (4.01); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ = 2.77 ppm (s, 3H), 8.00 (d, J = 9.1 Hz, 1H), 8.06 (s, 1H), 8.30 (dd, J = 9.1, 2.3 Hz, 1H), 8.80 (d, J = 2.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ = 26.9 ppm (s), 121.4 (d), 121.6 (d), 123.9 (d), 129.5 (d), 138.9 (s), 145.9 (s), 147.6 (s), 147.8 (s), 191.7 (s); MS (EI, 70 eV) *m*/*z* (%) = 221 (61) [M$^+$], 206 (100), 160 (57), 132 (18), 43 (16); HRMS calcd for $C_{10}H_7NO_3S$ 221.01464, found 221.01566.

Computational Method. Density functional theory calculations of the infinite periodic crystal structure were carried out with the CPMD package[15] using the experimentally determined lattice parameters together with periodic boundary conditions. The structures and positions of the water molecules were optimized using the PBE exchange and correlation functional in conjunction with Vanderbilt ultrasoft pseudopotentials[16] and a plane wave basis set truncated at 30 Ry. During geometry optimization, all atoms in the unit cell except for the water molecules were kept fixed at their experimentally determined positions. The electronic structure analysis, including ELF calculations,[17,18] at optimized geometry was performed using normconserving Goedecker pseudopotentials[19,20] and a 120 Ry plane wave cutoff.

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Supporting Information Available: General experimental methods; proton NMR spectra of new compounds; procedures for the synthesis of arylbutanones **5** by Heck reaction; DFT optimized atomic coordinates in the unit cell of the monohydrate of **8e**; crystallographic information file for **8e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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