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[3+2]-Cycloadditions of 2-Aminothioisomünchnones to Alkynes: Synthetic Scope and Mechanistic Insights

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Dedicated to Prof. J. Elguero on the occasion of his 65th birthday

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Abstract—This manuscript describes the regiospecific 1,3-dipolar cycloadditions of 2-aminothioisomünchnones (**1**–**3**) with methyl propiolate. The structure of compound **4** has been unequivocally determined by X-ray crystallography. Based on these experimental arguments and a theoretical rationale that supports the regiochemistry observed, a mechanistic pathway is discussed to account for the formation of pyridone or thiophene derivatives. The protocol has also been extended to the cycloadditions of aminothioisomünchnones derived from carbohydrates with dimethyl acetylenedicarboxylate to afford interesting glycosylaminoheterocycles.

Introduction

In recent years considerable attention has been focused on the formation of functionalized heterocyclic skeleta through [3+2]-cycloadditions of mesoionic rings.[1] Thus, 1-3-thiazolium-4-olates (commonly named thioisomünchnones),[2] which can easily be prepared from simple thioamides, contain a masked thiocarbonyl ylide dipole in their structure capable of undergoing 1,3-dipolar cycloadditions. Despite the considerable amount of research dealing with the chemistry of thioisomünchnones, the range of products accessible by means of cycloaddition reactions has remained somewhat narrow. In general, most thioisomünchnones react with electron-deficient alkenes to give stable cycloadducts which can further fragment to produce 2-pyridones after extrusion of hydrogen sulfide, while the reaction with acetylenic dipolarophiles gives rise to either thiophenes or 2-pyridones.[1] In previous studies concerning the preparation of optically active heterocycles, we have shown that bulky and rather rigid carbohydrate-appended thioisomünchnones react with acetylenic dipolarophiles to afford exclusively 2-pyridone derivatives.[3]

Nevertheless, during the course of our recent research we have also disclosed that thioisomünchnones **1**–**3** bearing an *N*-benzyl-*N*-methylamino group at C-2 exhibit a particular reactivity towards alkenes[4,5] and carbonyls.[6] The presence of such a dialkylamino substituent constitutes a key stereocontrolling factor and largely dictates the subsequent fragmentation pathway of cycloadducts. With these premises, it would be interesting to explore the dipolar cycloadditions of these 2-amino-substituted thioisomünchnones with alkynes. This full account describes our results in this area, which have also been extended to enantiomerically pure thioisomünchnones derived from carbohydrates. In addition, a mechanistic rationale of the steric course is also provided.

Results and Discussion

Synthetic studies

The reaction of thioisomünchnone **1**, having an electron-withdrawing substituent at C-3, with methyl propiolate in CH_2Cl_2 solution at room temperature for 3 h gave a mixture of pyridone and thiophene derivatives in 75 and 10% yield, respectively. However, cycloadditions of thioisomünchnones **2** and **3**, conducted under the same reaction conditions, afforded 2-pyridones in a regiospecific fashion (Scheme 1). The formation of thiophenes could not be observed at all after an inspection of crude samples by 400-MHz analysis.

The structures attributed to pyridones **4**, **6** and **7** are consistent with their spectroscopic data. The only proton present at the heterocyclic nucleus, H-4, exhibits downfield resonances (δ 8.09–8.12, singlet signals). This large deshielding should be caused by ring currents of the

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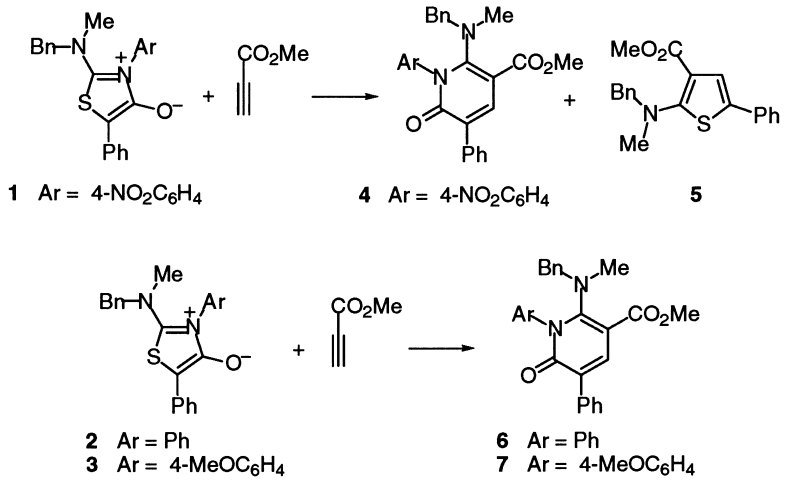
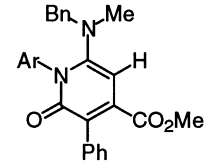


Scheme 1.

adjacent methoxycarbonyl and phenyl groups at C-5 and C-3, respectively. Similar chemical shifts have been found in other pyridones with the same substitution pattern.[3]

Although methyl propiolate is an unsymmetrically substituted dipolarophile, other regioisomers could not be detected. This fact excludes the alternative structures **8**–**10** in which a small anisotropic effect would otherwise be expected for H-5. On the other hand, aromatic protons of **4**, **6** and **7** at C-3 appear as multiplet signals, in agreement with a coplanar arrangement between that phenyl group and the heterocyclic moiety, which is only possible in the absence of substituents at C-4.



8 Ar = 4-$NO_2C_6H_4$
9 Ar = Ph
10 Ar = 4-$MeOC_6H_4$

The ^{13}C DEPT spectrum[7] also suggests that resonances assigned to C-4 ($\delta\sim140$) should correspond to a carbon atom with an attached hydrogen atom. Moreover, the structure of **4** was unequivocally established by X-ray diffraction analysis, thereby confirming the regiochemistry and atom connectivity (Fig. 1, see Experimental for diffraction details). The structure of thiophene **5** was assigned on the basis of its ^1H and ^{13}C NMR spectra, and assuming that a common cycloadduct led to both reaction products **4** and **5** (vide infra).

Next, we were interested in exploring the reactivity of thioisomünchnones derived from carbohydrates by employing *N*-methyl-D-glucamine (**11**) as a template. The sequential preparation of such mesoionics comprises three steps: (a) intermolecular coupling with an appropriate aryl isothiocyanate, (b) *O*-protection of the acyclic carbohydrate moiety, and (c) *mesoionization* of the resulting aryl thioureas with 2-chloro-2-phenylacetyl chloride in the presence of triethylamine.

The condensation of **11** with aromatic isothiocyanates was conducted in pyridine at room temperature for 1 h. Further

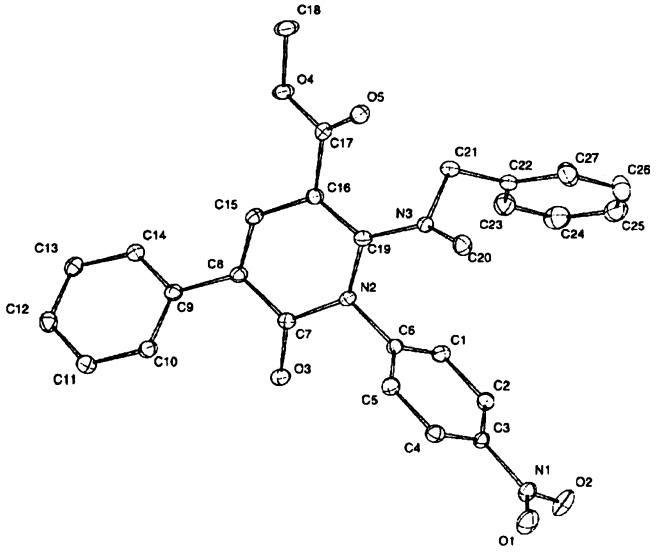
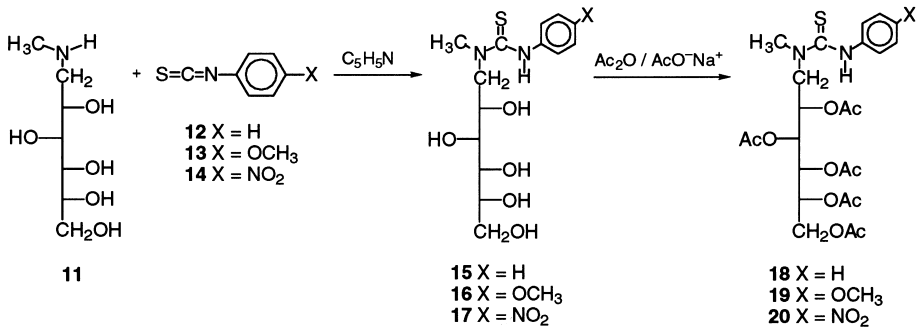


Figure 1. Solid-state structure of pyridone **4**.

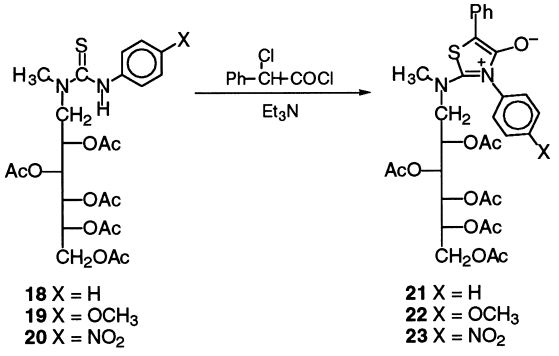


Scheme 2.

addition of diethyl ether led to crystallization of the corresponding thioureas in high yields (>85%), which could easily be purified by recrystallization from 96% aqueous ethanol. Conventional acetylation of hydroxyl groups at the acyclic side chain was accomplished by dissolving the aryl thioureas **15**–**17** in acetic anhydride and using melt sodium acetate as catalyst. Although the acetylation proceeded slowly at room temperature and required 7 days for completion, the *O*-protected derivatives **18**–**20** were isolated in good yields as crystalline materials and without competing side products (Scheme 2).

The unprotected thioureas **15**–**17** were fully characterized through their spectroscopic data and elemental analyses. Having demonstrated the identity of such intermediates, the formation of compounds **18**–**20** could also be carried out in a one-step protocol starting from **11** (see Experimental). The conversion of thioureas into mesoionic heterocycles can successfully be accomplished by means of two general procedures. On the one hand, the condensation of thioureas with 2-bromophenyl acetic acid under basic conditions followed by further cyclodehydration in hot acetic anhydride to afford 1,3-thiazolium-4-olate systems.[8] On the other hand, the direct coupling of an *N*-monosubstituted thioamide (e.g. thioureas **18**–**20**) with an α-haloacyl chloride in the presence of triethylamine causes the formation of **21**–**23** (Scheme 3).[9] The latter procedure is preferred since it avoids the chromatographic purification and isolation of intermediates, which in the present case are in fact diastereomeric mixtures, and the overall transformation can be achieved in a shorter reaction time.

Although compounds **21**–**23** can be isolated as solids or oily materials, they are not stable enough to be stored for several



Scheme 3.

days without appreciable decomposition. Alternatively, homogeneous solutions of these substances were reacted in situ with alkynes. Reactions with methyl propiolate were sluggish and we then turned our attention to a more reactive dipolarophile, dimethyl acetylenedicarboxylate (Scheme 4).

As expected, thioisomünchnones **21** and **22** afforded exclusively pyridone derivatives, **24** and **25**, respectively, and no trace of thiophenes could be detected by inspection of the reaction mixtures. Compounds **24** and **25** gave a negative sulfur test and their structures are consistent with their spectroscopic and analytical data. In particular, the presence of two aromatic rings and a diagnostic ^{13}C peak at $\delta \sim 102$, attributable to C-5,[3,10] could easily be identified in their NMR spectra.

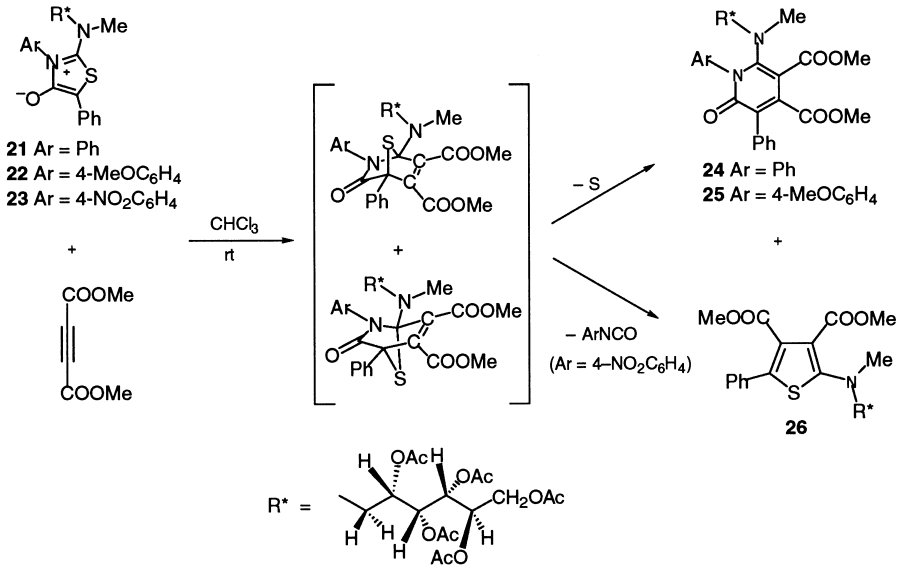
However, the coupling of **23** with dimethyl acetylenedicarboxylate under the same reaction conditions gave rise to a thiophene derivative (**26**) as the sole product, albeit it was isolated in moderate yield. This product gave a positive sulfur test and 4-nitrophenyl isocyanate could be identified as byproduct, in agreement with the accepted mechanistic hypothesis that accounts for the formation of thiophenes. Notably, all attempts to isolate or detect the transient cycloadducts during the cycloadditions of **21**–**23** failed, even when the reactions were conducted at 0°C.

Regioselectivity

We have investigated the reactions of thioisomünchnones **1**–**3** with methyl propiolate at the PM3 level[11] using the GAUSSIAN94 package,[12] to clarify the nature of this cycloaddition and the regiochemistry observed experimentally. Employing the background provided by the frontier orbital theory,[13] Table 1 depicts the energies and coefficients of the frontier orbitals.

We immediately learn from such data that the interaction $HOMO_{dipole}$–$LUMO_{dipolarophile}$ ($7.64 < \Delta E < 8.02$ eV) is more favorable than the opposite energy gap between $HOMO_{dipolarophile}$ and $LUMO_{dipole}$ ($9.76 < \Delta E < 10.18$ eV). Accordingly, the above cycloadditions are called *dipole-HOMO controlled* reactions or Sustmann's type I cycloadditions,[14] which look a little bit like a normal Diels–Alder reaction.

The HOMOs of **2** and **3** are brought closer in energy (−7.50 and −7.47 eV, respectively), whereas the HOMO of **1** is



Scheme 4.

Table 1. Energies and coefficients of the frontier orbitals for compounds **1**–**3** and methyl propiolate

Compound	Orbital	Energy (eV)	c_1	c_2	c_3	c_4	c_5
1	HOMO	−7.85	−0.19	−0.28	0.15	0.14	0.51
	LUMO	−1.81	−0.36	0.58	−0.30	−0.01	0.29
2	HOMO	−7.50	−0.18	−0.26	0.15	0.14	0.51
	LUMO	−1.39	−0.40	0.63	−0.37	−0.02	0.29
3	HOMO	−7.47	−0.21	−0.26	0.15	0.14	0.53
	LUMO	−1.81	−0.39	0.64	−0.38	−0.02	0.30
Methyl propiolate	HOMO	−11.57	0.00	0.00	0.00		
	LUMO	0.17	−0.60	−0.42	0.61		

lowered to −7.85 eV. This small difference, however, accounts for the higher reactivity of thioisomünchnones **2** and **3**, whose cycloadditions are complete within 1 h, while the reaction of **1** and methyl propiolate required 3 h for completion.

Next, the coefficients of the atomic orbitals were examined since they largely influence the regioselectivity.[13] Fig. 2 shows the two possible orientations of the cycloaddition of **1** with methyl propiolate. We have looked at the coefficients of the HOMO of the dipole and of the LUMO of the dipolarophile on the atoms at which bonding is to take place (C-5 of **1** and C-3 of methyl propiolate). Assuming that the predicted regioselection arises from the interaction between the larger coefficient on one component with the larger on the other, we need to look only at the left-hand combination in Fig. 2. Such an approach gives rise to an intermediate cycloadduct, which upon sulfur extrusion, effectively leads to the observed regioisomer. The other interaction disagrees with the experiment (Scheme 5).

Mechanistic considerations

The 1,3-dipolar cycloaddition of mesoionics with dipolarophiles should be occurring via the corresponding cycloadducts as intermediates, even though the latter substances could not be detected in the present study. The principles of orbital symmetry conservation, together with experimental considerations of reactivity and regioselectivity, and small solvent effects, all suggest a highly ordered transition state consistent with a concerted mechanism.[15,16] Nevertheless, the determination of transition states might be expected to provide a definite answer, although only calculations at a sufficiently high level will be a truly fair test of the energies of concerted, zwitterionic or diradical transition states.[17]

In principle, the formation of pyridones may take place either by a cheletropic process or a stepwise mechanism (Scheme 6). In both cases, the nature of the aryl substituent at the endocyclic nitrogen atom should be a prime factor controlling the stability of a concerted transition state or of a

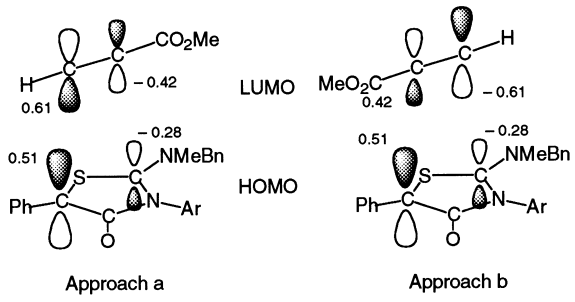
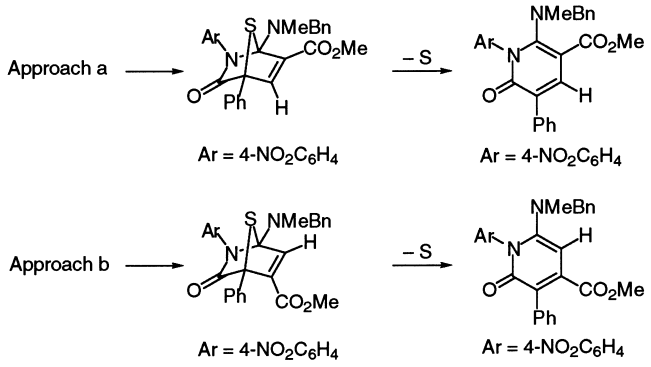
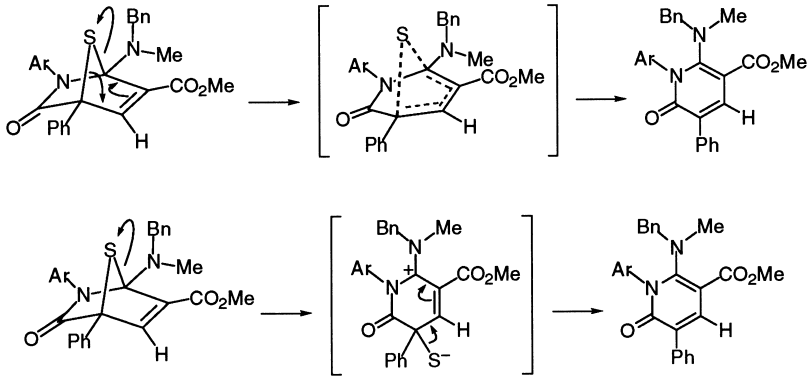


Figure 2.



Scheme 5.



Scheme 6.

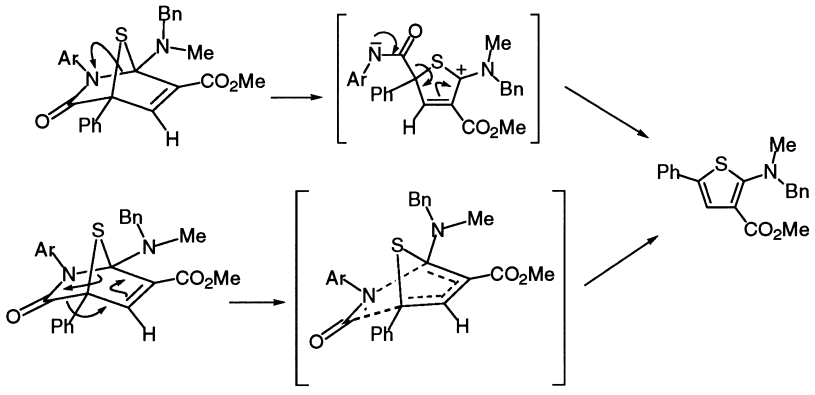
dipolar intermediate. Electron-donating groups will increase delocalization in a concerted mechanism or will spread the positive charge over more atoms.

In stark contrast, an electron-withdrawing substituent (e.g. 4-nitrophenyl) will stabilize a different dipolar intermediate or transition state, in which elimination of aryl isocyanate will compete favorably with the alternative carbon–sulfur scission (Scheme 7). Thus, the aryl substituent at C-3 of thioisomünchnones seems to be an important factor for cycloadduct cleavage. On the other hand, the stereoelectronic effect provided by the lone pair of the exocyclic *N*,*N*-dialkylamino substituent will spread the charge at the bridgehead carbon. The extended conjugation due to resonance, however, might disfavor a concerted cleavage. Further studies, including the search of transition structures for these cycloadditions with acetylenic and olefinic dipolarophiles are currently in progress.

Experimental

General methods

Melting points were determined on a capillary apparatus and are uncorrected. Optical rotations were measured at the sodium line at 18±2°C with a Perkin–Elmer 241 polarimeter. Analytical and preparative TLC were



Scheme 7.

performed on Merck 60 GF_{254} silica gel with monitoring by means of UV at 254 and 360 nm and iodine vapors. Flash chromatography[18] was performed with Merck 60 silica gel (400–230 mesh). IR spectra were recorded on a Perkin–Elmer 399 or a FT-IR Midac spectrometers. ^1H and ^{13}C NMR spectra were obtained with a Bruker AM 400 instrument at 400 and 100 MHz, respectively, in $CDCl_3$ (Me_4Si as internal standard) unless otherwise specified. Elemental analyses were recorded on a Lecco 932 analyzer at the *Universidad de Extremadura*, and by the *Servei de Microanàlisi del CSIC* at Barcelona, and the *Instituto de Investigaciones Químicas del CSIC* at Sevilla. High-resolution mass spectra (HRMS/CI^+) were carried out at the *Universidad de Córdoba*, Spain.

6-(*N*-Methyl)benzylamino-5-methoxycarbonyl-1-(4-nitrophenyl)-3-phenylpyridin-2-one (4) and 2-(*N*-methyl)-benzylamino-3-methoxycarbonyl-5-phenylthiophene (5). To a solution of 2-(*N*-methyl)benzylamino-3-(4-nitrophenyl)-5-phenyl-1,3-thiazolium-4-olate (**1**, 1.00 g, 2.4 mmol) in dry CH_2Cl_2 (13 mL) was added methyl propiolate (0.24 g, 2.8 mmol) and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the resulting crude was purified by flash chromatography (ethyl acetate–hexane, 1:3) to afford **4** (0.85 g, 75%) and **5** (0.03 g, 10%).

Compound **4**: yellow crystals; mp 149°C (Et_2O); IR (KBr) ν_{max} 1710, 1660, 1530, 1240, 900, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23 (d, 2H, aryl), 8.12 (s, 1H, H-4), 7.69–6.82 (m, 12H, aryl), 3.98 (s, 2H, CH_2Ph), 3.89 (s, 3H, CH_3O), 2.49 (s, 3H, CH_3N); ^{13}C NMR ($CDCl_3$) δ(165.2 (CO_2CH_3), 162.3 (C-2), 156.8 (C-6), 147.2, 144.3, 135.7, 135.4, 130.2, 128.6, 128.4, 128.3, 128.2, 128.0, 127.8, 124.2 (aryl), 140.0 (C-4), 126.9 (C-3), 105.5 (C-5), 59.2 (CH_2), 52.3 (CO_2CH_3), 40.0 (CH_3N). Anal. Calcd for $C_{27}H_{23}N_3O_5$: C, 69.07; H, 4.94; N, 8.95. Found: C, 69.11; H, 4.80; N, 8.94.

Compound **5**: yellow oil; IR ($CHCl_3$) ν_{max} 2940, 1700, 1510, 1430, 1350, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52–7.21 (11H, H-4, aryl), 4.54 (CH_2), 3.81 (CH_3O), 2.90 (CH_3N); ^{13}C NMR ($CDCl_3$) δ 166.1 (CO_2CH_3), 163.2 (C-2), 136.9, 134.0, 128.8, 128.5, 128.2, 127.5, 126.8, 124.8 (aryl), 124.4 (C-4), 128.8 (C-3), 113.4 (C-5), 62.1 (CH_2), 51.3 (CO_2CH_3), 42.4 (CH_3N). Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.22; H, 5.64; N, 4.15. Found: C, 71.11; H, 5.80; N, 3.94.

6-(*N*-Methyl)benzylamino-5-methoxycarbonyl-1,3-diphenylpyridin-2-one (6). To a solution of 2-(*N*-methyl)-benzylamino-3,5-diphenyl-1,3-thiazolium-4-olate (**2**, 0.50 g, 1.3 mmol) in dry CH_2Cl_2 (7 mL) was added methyl propiolate (0.13 g, 1.5 mmol) and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was treated with Et_2O to give the title compound as yellow crystals (0.50 g, 93%). Mp 123°C (Et_2O); IR (KBr) ν_{max} 1700, 1660, 1520, 1240, 900, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (s, 1H, H-4), 7.74–6.78 (m, 15H, aryl), 3.96 (s, 2H, CH_2), 3.87 (s, 3H, CH_3O), 2.46 (s, 3H, CH_3N); ^{13}C NMR ($CDCl_3$) δ 165.5 (CO_2CH_3), 162.7 (C-2), 157.5 (C-6), 139.6 (C-4), 138.6, 136.1, 135.9, 129.1, 128.6, 128.4, 128.0, 127.9, 127.5, 127.3 (aryl), 126.2 (C-3), 104.8 (C-5), 58.7 (CH_2), 52.0 (CO_2CH_3), 39.7 (CH_3N). Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 76.74; H, 5.50; N, 6.62.

6-(*N*-Methyl)benzylamino-5-methoxycarbonyl-1-(4-methoxyphenyl)-3-phenylpyridin-2-one (7). To a solution of 2-(*N*-methyl)benzylamino-3-(4-methoxyphenyl)-5-phenyl-1,3-thiazolium-4-olate (**3**, 0.50 g, 1.2 mmol) in dry CH_2Cl_2 (6.5 mL) was added methyl propiolate (0.12 g, 1.4 mmol) and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated to dryness and the further addition of Et_2O gave the title compound as yellow crystals (0.20 g, 44%). Mp 176°C (Et_2O); IR (KBr) ν_{max} 1700, 1640, 1500, 1230, 900, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09 (s, 1H, H-4), 7.72 (d, 2H, aryl), 7.38–6.88 (m, 12H, aryl), 3.96 (s, 2H, CH_2Ph), 3.86 (s, 3H, CO_2CH_3), 3.82 (s, 3H, CH_3O), 2.48 (s, 3H, CH_3N); ^{13}C NMR ($CDCl_3$) δ 165.6 (CO_2CH_3), 163.0 (C-2), 159.2 (aryl), 157.7 (C-6), 139.6 (C-4), 136.3, 136.1, 131.1, 129.8, 128.7, 128.5, 128.1, 128.0, 127.5, 127.4, 114.4 (aryl), 125.9 (C-3), 104.5 (C-5), 58.9 (CH_2), 55.5 (CH_3O), 52.0 (CO_2CH_3), 40.0 (CH_3N). Anal. Calcd for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.84; H, 5.73; N, 6.14.

General procedure for the preparation of *N′*-aryl-*N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-pentahydroxyhexyl-1-yl-*N*-methylthioureas (15–17)

To a suspension of *N*-methyl-D-glucamine (**11**, 1.0 g, 5.13 mmol) in pyridine (4.5 mL) was added the corresponding aryl isothiocyanate (5.13 mmol) and the reaction mixture was stirred at ambient temperature for 1 h. The resulting thioureas were isolated by addition of Et_2O and further purification by recrystallization from 96% aqueous EtOH.

***N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-Pentahydroxyhexyl-1-yl-*N*-methyl-*N′*-phenylthiourea (15).** White crystals were obtained in 87% yield, mp 100°C; $[\alpha]_D$=+12.5 (*c* 0.5, H_2O); IR (KBr) ν_{max} 3300, 1510, 1320, 1050 cm^{-1}; ^{13}C NMR (DMSO-d_6) δ 181.9 (C=S), 141.2, 128.2 (2C), 124.6, 124.1 (phenyl), 72.1, 71.7, 71.6, 69.8 (CHOH), 63.2 (CH_2OH), 56.1 (NCH_2), 40.1 (NCH_3). Anal. Calcd for $C_{14}H_{22}N_2O_5S$: C, 50.89; H, 6.71; N, 8.48; S, 9.70. Found: C, 50.74; H, 6.78; N, 8.56; S, 9.60.

***N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-Pentahydroxyhexyl-1-yl-*N*-methyl-*N′*-(4-methoxy)phenylthiourea (16).** White crystals were obtained in 92% yield, mp 120°C; $[\alpha]_D$=+9.0 (*c* 0.5, H_2O); IR (KBr) ν_{max} 3300, 1500, 1325 cm^{-1}; ^{13}C NMR (DMSO-d_6) δ 182.1 (C=S), 156.4, 134.1, 126.9, 113.4 (phenyl), 72.1, 71.9, 71.5, 69.7 (CHOH), 63.4 (CH_2OH), 56.1 (NCH_2), 55.4 (OCH_3), 40.1 (NCH_3). Anal. Calcd for $C_{15}H_{24}N_2O_6S$: C, 49.99; H, 6.71; N, 7.77; S, 8.89. Found: C, 49.87; H, 6.69; N, 7.84; S, 8.82.

***N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-Pentahydroxyhexyl-1-yl-*N*-methyl-*N′*-(4-nitro)phenylthiourea (17).** White crystals were collected in 83% yield, mp 155°C; $[\alpha]_D$=+15.5 (*c* 0.5, MeOH); IR (KBr) ν_{max} 3300, 1590, 1540, 1500, 1320 cm^{-1}; ^{13}C NMR (DMSO-d_6) δ 181.1 (C=S), 147.8, 142.0, 124.3 (2C), 122.1 (2C) (phenyl), 71.8, 71.5 (2C), 69.9 (CHOH), 63.4 (CH_2OH), 56.2 (NCH_2), 41.02 (NCH_3). Anal. Calcd for $C_{14}H_{21}N_3O_7S$: C, 44.79; H, 5.63;

N, 11.19; S, 8.54. Found: C, 44.73; H, 5.78; N, 11.24; S, 8.38.

General procedures for the preparation of *N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-pentaacetoxyhexyl-1-yl-*N*′-aryl-*N*-methylthioureas (18–20)

Method A: To a suspension of the corresponding aryl thiourea (**15**–**17**, 1.0 g) in acetic anhydride (14 mL), cooled at 0°C (external bath), was added a catalytic amount of melt sodium acetate (3 mg). The reaction mixture was allowed to warm to room temperature and then it was kept under such conditions till TLC analysis (ethyl acetate–hexane 3:2) revealed the disappearance of the starting material and the formation of a single product (~7 days). The mixture was poured into ice-water and the resulting solid was recrystallized from 96% aqueous EtOH.

Method B: To a suspension of *N*-methyl-D-glucamine (**11**, 1.0 g, 5.13 mmol) in pyridine (5 mL) was added an aryl isothiocyanate (5.13 mmol) and the mixture was stirred at room temperature for 1 h. Then, acetic anhydride (25 mL) and a catalytic amount of sodium acetate (3 mg) and the reaction mixture was kept for 7 days under these conditions. It was poured into ice-water, the white solids were collected by filtration and recrystallized from 96% aqueous EtOH.

***N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-Pentaacetoxyhexyl-1-yl-*N*-methyl-*N*′-phenylthiourea (18).** Either method gave the title compound in 65% yield as white crystals with mp 105°C; $[\alpha]_D=-39.0$ (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 1750, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.30 (m, 5H, phenyl), 5.78 (m, 1H, H-2′), 5.43 (m, 1H, H-4′), 5.39 (m, 1H, H-3′), 5.06 (m, 1H, H-5′), 4.29–4.08 (m, 4H, H-1′, H-1″, H-6′, H-6″), 3.29 (s, 3H, *N*–CH_3), 2.14 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 186.4 (C=S), 170.4, 169.8, 169.7, 169.7, 169.5, 168.6 (C=O), 140.0, 129.2, 129.0, 128.0 (phenyl), 69.5, 68.9, 68.4, 67.9 (CHOAc), 61.3 (CH_2OAc), 55.6 (CH_2N), 41.2 (CH_3N), 20.7, 20.7, 20.6, 20.4, 20.2 (CH_3CO). Anal. Calcd for $C_{24}H_{32}N_2O_{10}S$: C, 53.33; H, 5.92; N, 5.18; S, 5.92. Found: C, 53.42; H, 5.87; N, 4.93; S, 5.39.

***N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-Pentaacetoxyhexyl-1-yl-*N*-methyl-*N*′-(4-methoxy)phenylthiourea (19).** White crystals were obtained in 75% (Method A) and in 86% yield (Method B), having mp 120°C; $[\alpha]_D=-29.0$ (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 1750, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26–6.89 (m, 4H, phenyl), 5.75 (m, 1H, H-2′), 5.42–5.36 (m, 2H, H-4′, H-3′), 5.03 (m, 1H, H-5′), 4.28–4.08 (m, 4H, H-1′, H-1″, H-6′, H-6″), 3.81 (s, 3H, OCH_3), 3.28 (s, 3H, NCH_3), 2.13 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.02 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 186.8 (C=S), 170.5, 169.9, 169.8 (2C), 168.9 (C=O), 159.2, 133.0, 129.3 (2C), 114.4 (2C) (phenyl), 69.6, 68.7, 68.5, 68.0 (CHOAc), 61.3 (CH_2OAc), 55.5 (CH_2N), 55.4 (OCH_3), 41.1 (CH_3N), 20.8 (2C), 20.7 (2C), 20.4 (CH_3CO). Anal. Calcd for $C_{25}H_{34}N_2O_{11}S$: C, 52.62; H, 6.01; N, 4.91; S, 5.62. Found: C, 52.64; H, 5.91; N, 4.65; S, 5.18.

***N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-Pentaacetoxyhexyl-1-yl-*N*-methyl-*N*′-(4-nitro)phenylthiourea (20).** Either procedure (A or B) gave the title compound in 85% yield with mp 140°C; $[\alpha]_D=-45.5$ (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 1750, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.27–7.53 (m, 4H, phenyl), 5.80 (m, 1H, H-2′), 5.46 (m, 1H, H-4′), 5.40 (m, 1H, H-3′), 5.06 (m, 1H, H-5′), 4.30 (m, 2H, H-1′, H-6′), 4.11 (m, 2H, H-1″, H-6″), 3.22 (s, 3H, NCH_3), 2.13 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.04 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 185.3 (C=S), 170.5, 170.1, 169.8 (2C), 168.4 (C=O), 146.1, 144.9, 126.9 (2C), 124.6 (2C) (phenyl), 69.7, 68.9, 68.7, 68.3 (CHOAc), 61.3 (CH_2OAc), 56.3 (CH_2N), 41.6 (CH_3N), 20.8, 20.8, 20.7 (2C), 20.5 (CH_3CO). Anal. Calcd for $C_{24}H_{31}N_3O_{12}S$: C, 49.23; H, 5.34; N, 7.18; S, 5.47. Found: C, 49.36; H, 5.36; N, 6.77; S, 4.79.

6-[*N*-Methyl-*N*-(2*S*,3*R*,4*S*,5*S*)-2′,3′,4′,5′,6′-pentaacetoxyhexyl-1-yl]amino-4,5-dimethoxycarbonyl-1,3-diphenylpyridin-2-one (24). To a solution of *N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-pentaacetoxyhexyl-*N*-methyl-*N*′-phenylthiourea (**18**, 1.0 g, 1.85 mmol) in dry $CHCl_3$ (20 mL) was added 2-chloro-2-phenylacetyl chloride (0.88 mL, 5.5 mmol). The reaction mixture was refluxed for 3 h, evaporated under reduced pressure, and the residue was washed with Et_2O. The latter was dissolved in $CHCl_3$ (40 mL), Et_3N (0.5 mL) was added, and the mixture was refluxed for 10 min. The resulting orange solution was washed repeatedly with distilled water, dried over anhydrous $MgSO_4$, and evaporated to dryness to give an oil. This substance was dissolved in dry $CHCl_3$ (10 mL), dimethyl acetylenedicarboxylate (0.25 mL, 2.0 mmol) was added, and the reaction mixture was kept at room temperature for 1 h. TLC analysis (Et_2O–hexane 4:1) revealed the formation of a new compound, which could be isolated after addition of *n*-hexane, filtration, and recrystallization from $CHCl_3$–ethyl acetate (0.85 g, 60%). Mp 200°C; $[\alpha]_D=+6.0$ (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 1745, 1650, 1370, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.26 (m, 10H, phenyl), 5.29 (m, 2H, H-3′, H-4′), 5.04–5.02 (m, 2H, H-2′, H-5′), 4.27 (m, 1H, H-6′), 4.12 (dd, 1H, *J*=5.8, 12.5 Hz, H-6″), 3.83 (s, 3H, $COOCH_3$), 3.56 (s, 3H, $COOCH_3$), 2.75 (s, 4H, H-1′, NCH_3), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.57 (s, 1H, H-1″); ^{13}C NMR ($CDCl_3$) δ 170.5, 170.0, 169.8, 169.7, 167.2, 165.1, 162.4, 155.1, 142.9, 137.7, 133.9, 129.6, 129.2, 129.0, 128.4, 128.2, 128.0, 127.8, 125.8, 102.7 (C-5), 69.5, 68.9, 68.8, 68.6 (CHOAc), 61.6 (CH_2OAc), 53.5 (CH_2N), 52.6 ($COOCH_3$), 52.2 ($COOCH_3$), 42.1 (CH_3N), 20.9, 20.7 (2C), 20.6, 20.5. Anal. Calcd for $C_{38}H_{42}N_2O_{15}$: C, 59.53; H, 5.48; N, 3.65. Found: C, 59.76; H, 5.62; N, 3.73.

6-[*N*-Methyl-*N*-(2*S*,3*R*,4*S*,5*S*)-2′,3′,4, ′5′,6′-pentaacetoxyhexyl-1-yl]amino-4,5-dimethoxycarbonyl-1-(4-methoxy)-phenyl-3-phenylpyridin-2-one (25). The title compound was prepared from *N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-pentaacetoxyhexyl-*N*-methyl-*N*′-(4-methoxy)phenylthiourea (**19**) in 22% yield in following the procedure described above for the preparation of **24**. Mp 130°C (Et_2O); $[\alpha]_D=+13.0$ (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 1740, 1340, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–6.95 (m, 9H, phenyl), 5.30 (m, 2H, H-4′, H-3′), 5.07–5.01 (m, 2H, H-2′, H-5′), 4.27 (m, 1H, H-6′), 4.11 (dd, 1H, *J*=5.7, 12.4 Hz, H-6″), 3.81 (s, 3H, $COOCH_3$), 3.80 (s, 3H, OCH_3), 3.53 (s, 3H, $COOCH_3$), 2.75 (s, 3H,

NCH_3), 2.07–2.01 (m, 16H, H-1′, 5 OAc), 1.71 (m, 1H, H-1″); ^{13}C NMR ($CDCl_3$) δ 170.5, 170.0, 169.8, 169.7, 167.2, 165.1, 162.6, 159.2, 155.2, 142.7, 134.0, 130.1, 129.6, 128.0, 127.8, 125.6, 102.7 (C-5), 69.5, 68.9, 68.8, 68.6 (CHOAc), 61.6 (CH_2OAc), 55.4 (OCH_3), 53.3 (NCH_2), 52.5 ($COOCH_3$), 52.2 ($COOCH_3$), 42.1 (CH_3N), 23.0, 20.9, 20.7, 20.6, 20.4. HRMS (CI^+) found: 796.269084 ($C_{39}H_{44}N_2O_{16}$ requires 796.268062), Δ=1.3 ppm.

3,4-Dimethoxycarbonyl-5-[*N*-(2*S*,3*R*,4*S*,5*S*)-2′,3′,4′,5′,6′-pentaacetoxyhexyl-1-yl]methylamino-2-phenylthiophene (26). This substance was obtained from *N*-(2*S*,3*R*,4*S*,5*S*)-2,3,4,5,6-pentaacetoxyhexyl-*N*-methyl-*N*′-(4-nitro)phenylthiourea (**20**) in 43% yield as an oil, in following the above-mentioned procedures for **24** and **25**, and after purification of the final residue by flash chromatography (Et_2O–hexane 4:1). IR (neat) ν_{max} 1740–1700, 1500, 1430, 1360, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40–7.27 (m, 5H, phenyl), 5.36 (m, 3H, H-2′, H-3′, H-4′), 5.05 (m, 1H, H-5′), 4.27 (dd, 1H, *J*=2.5, 12.5 Hz, H-6′), 4.13 (dd, 1H, *J*=5.2, 12.5 Hz, H-6″), 3.82 (s, 3H, $COOCH_3$), 3.78 (m, 1H, H-1′), 3.74 (s, 3H, $COOCH_3$), 3.47 (dd, 1H, *J*=2.6, 15.2 Hz, H-1″), 2.99 (s, 3H, NCH_3), 2.17 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.97 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 170.5, 170.1, 169.8, 169.7, 166.1, 163.1, 132.5, 130.8, 129.3, 128.6, 128.2, 114.5, 69.1, 68.7 (2C), 68.5, 61.4 (CH_2OAc), 57.2 (CH_2N), 52.3 ($COOCH_3$), 51.8 ($COOCH_3$), 43.9 (CH_3N), 30.9, 20.6 (3C), 20.4. HRMS (CI^+) found: 679.193665 ($C_{31}H_{37}NO_{14}S$ requires 679.193477), Δ=−0.3 ppm.

X-Ray crystallographic data for compound 4[19]

Yellow prisms from Et_2O, FW=469.48 for $C_{27}H_{23}N_3O_5$; data and diffraction parameters were obtained for a crystal with dimensions 0.40×0.30×0.20 mm^3 using MoKα (λ=0.71073 Å) at 150(2) K. Crystal system: triclinic, space group: *P*-1; unit cell dimensions: *a*=10.0971(4) Å, *b*=10.3866(3) Å, *c*=13.1345(5) Å, α=99.618(2)°, β=101.5257(16)°, γ=116.2341(18)°; *V*=1158.45(7) $Å^3$; *Z* (molecules/unit cell)=2; density (calcd): 1.346 Mg m^{-3}; μ (absorption coefficient): 0.094 mm^{-1}; *F*(000)=492; θ range for data collection: 3.19–25.03°; index ranges: $-12 \le h \le 11$, $-12 \le k \le 12$, $-15 \le l \le 15$; collected reflections: 11 909, independent reflections: 4086 [R_{int}=0.0348]; completeness to θ=25.03°: 99.6%; maximum and minimum transmission: 0.9814 and 0.9633; data/restraints/parameters: 4086/0/409; GOF (goodness-of-fit on F^2): 1.040; final *R* indices [$F^2 > 2\sigma(F^2)$] : *R*1=0.0439, *wR*2=0.1177; final *R* indices (all data): *R*1=0.0567, *wR*2=0.1254; extinction coefficient: 0.018(4); $\Delta\rho_{max}$ and $\Delta\rho_{min}$ (largest diff. peak and hole): 0.834 and −0.220 e $Å^{-3}$; refinement method: full-matrix least-squares on F^2.

Data collection was performed using a Enraf Nonius KappaCCD diffractometer. The structure was solved by direct methods with the SHELXS97 program,[20] while refinement was carried out on F^2 by application of the SHELXL97 program.[21] Absorption correction was accomplished by means of SORTAV.[22] All hydrogen atoms were located from the difference map and fully refined.

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