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From Thienodiazepinediones to Thienopyridinones: Flexible Synthesis of Substituted Thieno[3,2-*e*][1,4]diazepinones and 6-Aminothieno[3,2-*b*]pyridinones

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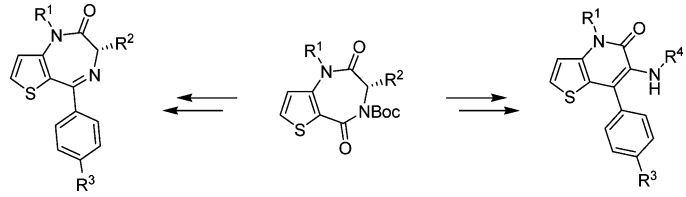

N-Substituted thienodiazepinedione opening with a series of organomagnesium bromides allowed the subsequent cyclization to the seven-membered ring thieno[3,2-*e*][1,4]diazepinone in 52−99% yields or to the six-membered ring thieno[3,2-*b*]pyridinones in 45−55% yields. Effective syntheses introducing considerable diversity onto these valuable scaffolds are described.

Introduction

Benzo[1,4]diazepin-2-ones and benzo[*b*]pyridin-2-ones (also referred to as quinolin-2(1*H*)-ones) are two privileged structures[1,2] which have attracted considerable attention in the design of biologically active molecules.[3−9] The chemistry developed around these two important scaffolds has contributed to the emergence of the useful thiophene isosters, namely the thieno[1,4]diazepin-2-ones and the thieno[*b*]pyridin-2-ones series. Clotiazepam (brand name Trecalmo) is a thienodiazepine marketed drug with anxiolytic, anticonvulsant, sedative, and muscle relaxant properties (Figure 1).[10,11] Ticlopidine (trade name Ticlid) and Clopidogrel (trade names Plavix and Clopilet) are two antiplatelet drugs derived from the thieno[*c*]pyridine skeleton, often used in the treatment of coronary artery disease, peripheral vascular disease, and cerebrovascular disease.[12] Moreover, thieno[*b*]pyridin-2-one derivatives have found various biological applications as new AMP-activated protein Kinase

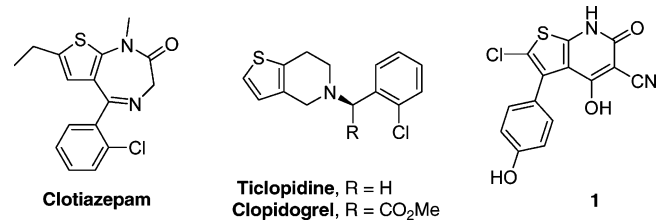

FIGURE 1. Structures of biologically important thieno[2,3-*e*]diazepine and thieno[2,3-*c*] or [2,3-*b*]pyridine compounds.

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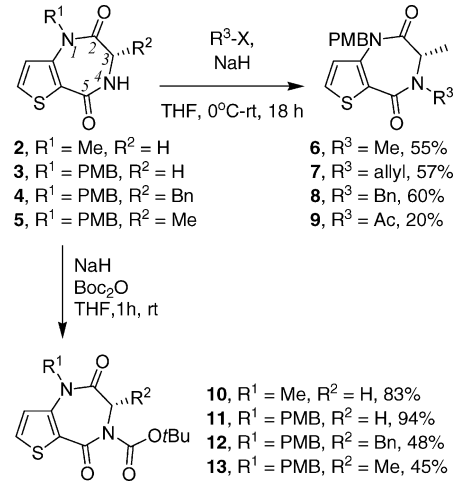
regulators (compound **1**) for the treatment of diabetes, metabolic syndrome, and obesity (Figure 1),[13] as inhibitors of macrophage migration inhibitory factor (MIF) in the field of immune related disorders or tumor associated angiogenesis,[14] as potent and selective p38 MAP Kinase inhibitors,[15] as cytoprotectants and inhibitors of [^{3}H]glycine binding to the *N*-methyl-D-aspartate (NMDA) receptor,[16] and as cholesterol acyl transferase inhibitors for the treatment of hypercholesterolemia or atherosclerosis.[17]

Since most synthetic routes described in the literature refer to the [2,3] type fusion between the thiophene and these seven- or six-membered heterocycles, access to the isomeric [3,2] type fusion is a more intricate task. In this context, we have recently described a general synthetic protocol to generate new thieno[3,2-*e*]diazepine-2,5-diones by regioselective ring-opening of thieno-[3,2-*d*][1,3]oxazine-2,4-dione (or 2-thiaisatoic anhydride)[18] by α-amino acids, followed by intramolecular cyclocondensation.[19] This methodology was further extended to the solid phase with *N*-alkylated α-amino acids leading to *C*3,*N*4-disubstituted thieno[3,2-*e*]diazepinediones.[20] In our ongoing interest for the development of focused heterocyclic libraries, we present herein further diversification of our privileged scaffold, by the access to new *C*5-arylated thieno[3,2-*e*]diazepin-2-ones **16** and **17**.

In this vein, the commonly employed synthetic route to *C*5-arylated benzo[1,4]diazepines starts from benzophenone derivatives. The major limitation of this methodology is the establishment of a C-5 substituent at an early stage in the synthesis, which is not ideal for the preparation of analogues containing diversity at this position. So far, two pathways have appeared to introduce C-5 diversity onto the benzo[1,4]diazepine-2,5-dione motif. The first selectively converts the benzodiazepinedione to the monoimidoyl chloride by treatment with phosphorus oxychloride ($POCl_3$) and *N*,*N*-dimethylaniline at reflux for 5 h.[21] Subsequent Suzuki cross-coupling allowed the introduction of a wide variety of aromatic and heteroaromatic substituents.[22] However, the imidoyl chloride isolation is fastidious and the product was found to be unstable if not allowed to react within a few hours. The second method was reported in 1980 for a new synthesis of diazepam, where the action of phenylmagnesium chloride on a 4-acetyl-benzodiazepinedione gave the corresponding benzophenone, which was treated with an excess of hydroxylamine hydrochloride in pyridine to provide the deacetylated oxime, which was then cyclized back to the 7-chloro-1-methyl-5-phenyl-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one (or diazepam) by action of aqueous alcoholic $NaHSO_3$.[23] To our knowledge, only a few accounts of C-5 diversification of the thieno[3,2-*e*]diazepine scaffold were reported, all from (3-aminothiophen-2-yl)phenylmethanone intermediates.[24,25]

SCHEME 1. *N*4-Substitution of thienodiazepinediones



Results and Discussion

In respect to literature precedents and in the context of our latest methodology to access thieno[3,2-*e*][1,4]diazepines, our efforts were converged toward the modification of the N-4, C-5 lactam of the thienodiazepine. Our first attempts to diversify the C-5 carbonyl of the thienodiazepine were carried out with $POCl_3$. Unfortunately, in our hands, these assays were unsuccessful in forming the corresponding imidoyl chloride. Therefore, our efforts were directed toward the use of Grignard reagents on *N*4-acylated thienodiazepinediones. To react adequately, the *N*4-substitution of thieno[3,2-*e*][1,4]diazepinediones **2** was first studied. Further diversification of the thieno[3,2-*e*][1,4]diazepinedione **2** can be introduced at the N-4 position of the diazepine ring by a different means than direct cyclization of the appropriate *N*-alkylated α-amino acid (α-aa).[20] Successful alkylation of **5** was rendered possible with the nucleophilic substitution of alkyl halides (MeI, allylCl, BnBr) in the presence of an inorganic base (like NaH or LiHMDS), in THF, at 0 °C to room temperature, for 18 h leading to diazepines **6**−**8** in 55% to 60% yields (Scheme 1). Acylation of **5** with acetyl chloride also furnished the disubstituted thienodiazepinedione **9**, but in a low yield of 20%. These results provided evidence of feasible *N*4-substitution of *N*1-alkylated thienodiazepinediones. Recently, the use of the *tert*-butyloxycarbonyl (Boc) group was described for the acylation of a benzodiazepine.[26] Since *N*4-Boc protection would provide a profitable electro-withdrawing effect for subsequent Grignard reactions, carbamate protection of the *N*4-thienodiazepines derived from glycine **2**−**3**, phenylalanine **4**, and alanine **5** were prepared by using di-*tert*-butyl dicarbonate (Boc_2O) and sodium hydride in THF at room temperature (Scheme 1). In sum, the acylation was more effective when the C-3 position of the diazepine was unsubstituted (**10** (83%), **11** (94%)) rather than comprised of an amino acid side chain ((**12** (48%), **13** (45%)). A similar observation was reported with the case of a *C*3-methyl benzo-

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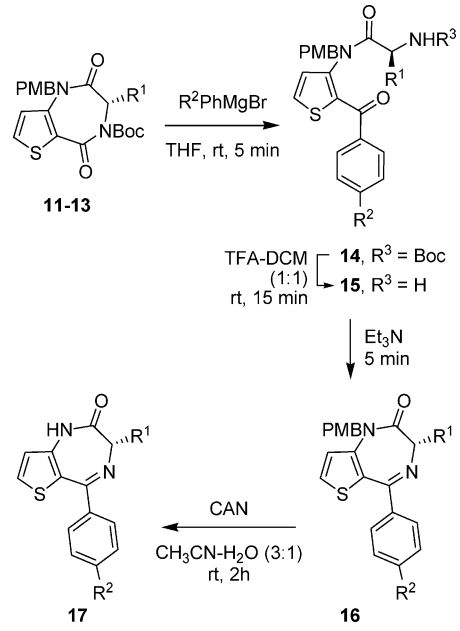
SCHEME 2. Synthesis of 5-Arylthieno[3,2-*e*][1,4]diazepinones 16 and 17



diazepine.[23] Most of these *C*3,*N*4-disubstituted thienodiazepines are sterically hindered and gave a mixture of two conformers on the ^{1}H and ^{13}C NMR spectra at room temperature, which were simplified by gradual heating (20 to 70 °C) of the deuterated solution during NMR acquisitions.

With the Boc protected thienodiazepines **10**−**13** in hand, it was now possible to diversify the C-5 carbonyl by treatment with a Grignard reagent. Our first attempt was initiated with diazepine **11** to afford the ketone **14a** by a rapid exothermic carbon−carbon bond formation using phenylmagnesium bromide in THF at room temperature, in 66% yield (Scheme 2). The alkoxymagnesium bromide intermediate was converted to the ketone **14a** after opening of the diazepine ring by rupture of the N-4, C-5 bond. The Grignard reagent's attack proceeds with good selectivity onto the C-5 vs. Boc carbonyls of the thienodiazepine **11**, resulting mainly in the formation of the corresponding ketone **14a** as well as some deprotected diazepine **3**, which was recuperated at the purification step. This observation was previously reported with benzodiazepines bearing different acyl groups (such as trifluoroacetyl, propionyl, *n*-butyroyl, and isobutyroyl),[23] but was not formerly cited with the Boc group.[26] In the next step, the amine **15a** was obtained after Boc removal, using 50% TFA in DCM at room temperature for 15 min, without affecting the stability of the orthogonal *p*-methoxybenzyl (PMB) group. Intramolecular cyclization of **15a** was then performed by addition of a non-nucleophilic base like triethylamine to form the seven-membered ring **16a**, which was purified by flash column chromatography[27] and isolated in 88% yield.

To validate this methodology, thienodiazepines **11**−**13** were submitted to Grignard reactions in the presence of *p*-chloro-, *p*-methoxy-, and phenyl magnesium bromides. Restitution of thienodiazepines **4** and **5** from the attack at the Boc carbonyl was not observed by LC-MS at 214 nm with the diazepines derived from phenylalanine **12** or alanine **13**, probably due to the steric hindrance or the electrodonating effect of these amino acid side chains. The resulting ketones **14** were no longer isolated but rather directly reacted in the next two steps to form the corresponding 1-(4-methoxybenzyl)-5-aryl-thieno[3,2-*e*][1,4]-diazepin-2-ones **16** isolated in medium to good yields of 58−99% over three steps (Table 1).

TABLE 1. 5-Arylthieno[3,2-*e*][1,4]diazepinones 16 and 17

entry	R^1	R^2	yield (%)
16a	H	H	58[a]
16b	H	OMe	62[a]
16c	H	Cl	66[a]
16d	Bn	H	99[a]
16e	Bn	OMe	99[a]
16f	Bn	Cl	99[a]
16g	Me	H	86[a]
16h	Me	OMe	71[a]
17a	H	H	54
17b	H	OMe	60
17c	H	Cl	52
17d	Bn	H	79
17e	Bn	OMe	85
17f	Bn	Cl	89
17g	Me	H	75
17h	Me	OMe	80

[a] Yields over 3 steps from diazepine **11**, **12**, or **13**.

Removal of the PMB group from the thienodiazepine was effectively performed by using an excess of ammonium cerium(IV) nitrate ($Ce(NH_4)_2(NO_3)_6$), referred to as CAN, in a mixture of CH_3CN-H_2O for 2 h at room temperature (Scheme 2).[28,29] Therefore, thieno[1,4]diazepines **17a**−**h** were recovered in pure form in 52−89% yields (Table 1).

Access to thienodiazepines **16** from ketones **14** by cyclocondensation led us to envisage an alternative synthetic pathway to produce six-membered heterocycles. Indeed, with the *N*-Boc-ketones **14** derived from glycine in hand, we were in a position to deprotonate the vicinal methylene instead of deprotecting the Boc group. Deprotonation of ketones **14a**−**c** and **18** was carried out with potassium *tert*-butoxide (KO*t*Bu) in THF for 30 min at room temperature and permitted condensation to the hydroxy six-membered ring **19** (Scheme 3). In a different way than with the diazepine formation, the six-membered rings were formed without spontaneous dehydration. Therefore, compound **19** was completely converted to the aromatic pyridinones **20**, in the *N*-PMB and the *N*-Me series, by using an excess amount of *p*-TsOH. After this one-pot three-step process, *tert*-butyl-4,5-dihydro-5-oxo-7-arylthieno[3,2-*b*]pyridin-6-ylcarbamate **20** was purified by flash column chromatography and isolated in yields of 45−55% (Table 2). The deficient Grignard selectivity of attack at the C-5 carbonyl of the thienodiazepines **10**−**11** (vs. the Boc group) as well as the partial hydrolysis of pyridinone **20** back to pyridinone **19** during the purification step contributed to lower the yield of this six-membered heterocycle series.

Access to this valuable scaffold pushed us to study its reactivity. Thus, a preliminary experiment to illustrate the use of this new strategy was initiated with an isocyanate. The Boc group was readily cleaved from **20b** with a 50% TFA solution in DCM, and after evaporation of the volatile material, acylation of amine **21** with a representative *p*-chlorophenylisocyanate in DCM proceeded smoothly to give urea **22** in 62% yields (Scheme 4).

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SCHEME 3. Synthesis of 6-Amino-7-arylthieno[3,2-*b*]pyridinone Analogues 20

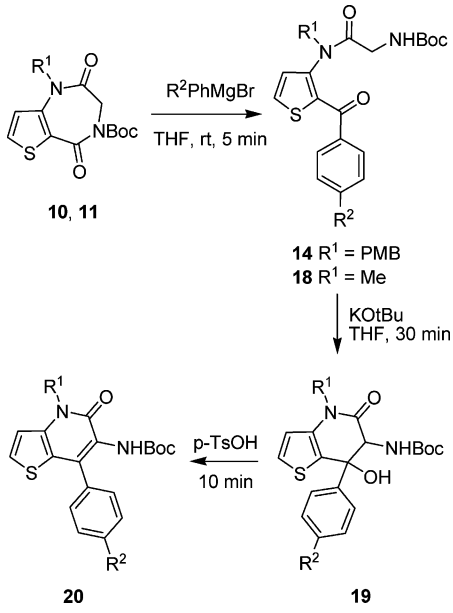
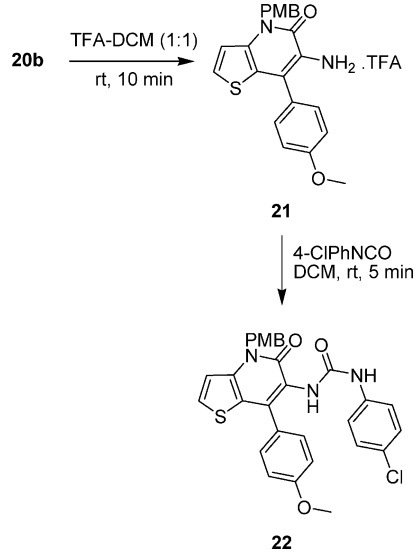


TABLE 2. 6-Amino-7-arylthieno[3,2-*b*]pyridinone Analogues 20

entry	R^1	R^2	yields (%)
20a	PMB	H	52
20b	PMB	OMe	47
20c	PMB	Cl	45
20d	Me	H	51
20e	Me	OMe	49
20f	Me	Cl	55

SCHEME 4. Amino Substitution of 6-Amino-7-arylthieno[3,2-*b*]pyridinone 20b



Conclusions

In conclusion, it was demonstrated that thienodiazepinediones can also be substituted at their N-4 position by alkylation (with alkyl halides) or acylation (with acetyl chloride or Boc_2O). Subsequently, diversification of their C-5 position can be achieved rapidly in three steps to furnish 5-arylthieno[3,2-*e*][1,4]diazepin-2-one **16** in 58−99% yields. Furthermore, from the same ketone intermediates **14**, access to 6-amino-7-arylthieno[3,2-*b*]pyridin-5-ones **20** was described in 45−55% yields. Considering the utility of thienodiazepines and thienopyridinones, the scope of these reactions is now under further investigation in our laboratories.

Experimental Section

Typical Procedure for Alkylation of *N*(4)-Diazepinediones 5.[20] A stirring solution of thienodiazepinedione **5** (0.100 g, 0.32 mmol) in THF (10 mL) was treated with NaH 60% in oil (0.025 g, 0.64 mmol) at 0 °C for 5 min. MeI (0.04 mL, 0.64 mmol) is added to the stirring suspension and agitated to rt for 18 h. The volatile material is evaporated and the residue is partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue is further purified by flash chromatography. Note: Conformers impede the formation of sharp signals on the ^1H NMR spectra at rt. Method A for the retention time refers to an HPLC method that is summarized in the Supporting Information.

(*S*)-1-(4-Methoxybenzyl)-3,4-dihydro-3,4-dimethylthieno[3,2-*e*][1,4]diazepine-2,5-dione (6): yield 55%; beige solid, mp 112−114 °C; $[\alpha]^{20}_D$ 29.4 (*c* 0.1, DMSO); ^1H NMR ($CDCl_3$) δ 7.42 (d, 1H, J = 5.4 Hz), 7.09 (d, 2H, J = 8.5 Hz), 6.86 (d, 1H, J = 5.3 Hz), 6.82 (d, 2H, J = 8.6 Hz), 5.13 (d, 1H, J = 15.3 Hz), 4.87 (d, 1H, J = 15.3 Hz), 4.37 (quad, 1H, J = 7.0 Hz), 3.77 (s, 3H), 3.08 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.3, 163.6, 159.2, 140.9, 130.3, 128.7, 128.3, 125.9, 121.2, 114.4, 55.4, 52.6, 50.4, 29.8, 13.4; HRMS calcd for $[M + H^+]$ $C_{17}H_{19}N_2O_3S$ 331.1116, found 331.1097; R_t 2.31 (method A); R_f 0.6, $CHCl_3$−AcOEt (1:1).

(*S*)-1-(4-Methoxybenzyl)-4-allyl-3,4-dihydro-3-methylthieno[3,2-*e*][1,4]diazepine-2,5-dione (7): yield 57%; beige solid, mp 98−100 °C; $[\alpha]^{20}_D$ 9.6 (*c* 0.2, DMSO); ^1H NMR (DMSO-d_6) δ 7.82 (d, 1H, J = 5.4 Hz), 7.25 (br s, 1H), 7.06 (d, 2H, J = 8.1 Hz), 6.82 (d, 2H, J = 7.6 Hz), 5.75 (m, 1H), 5.3−5.06 (m, 4H), 4.47−4.32 (m, 2H), 3.92 (m, 1H), 3.69 (s, 3H), 1.47−1.17 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 168.9, 163.6, 158.9, 140.9, 134.4, 131.1, 129.2, 128.7, 122.5, 116.9, 114.3, 55.4, 52.5, 48.5, 43.8, 13.5; HRMS calcd for $[M + H^+]$ $C_{19}H_{21}N_2O_3S$ 357.1273, found 357.1271; R_t 2.59 (method A); R_f 0.6, $CHCl_3$−AcOEt (9:1).

(*S*)-1-(4-Methoxybenzyl)-4-benzyl-3,4-dihydro-3-methylthieno[3,2-*e*][1,4]diazepine-2,5-dione (8): yield 60%; beige solid, mp 66−68 °C; $[\alpha]^{20}_D$ 73.6 (*c* 0.1, DMSO); ^1H NMR (DMSO-d_6) δ 7.85 (d, 1H, J = 5.4 Hz), 7.35−7.17 (m, 6H), 6.97 (d, 2H, J = 8.4 Hz), 6.79 (d, 2H, J = 8.4 Hz), 5.26 (m, 1H), 4.88 (m, 2H), 4.51 (m, 2H), 3.69 (s, 3H), 1.43 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 168.2, 163.6, 158.4, 140.2, 138.1, 130.9, 128.6, 128.2, 127.8, 127.1, 126.9, 124.7, 122.1, 113.9, 55.0, 52.3, 47.9, 44.5, 13.5; HRMS calcd for $[M + H^+]$ $C_{23}H_{23}N_2O_3S$ 407.1429, found 407.1405; MS (ESI, *m*/*z*) 407.2 $[M + H]^+$; R_t 2.90 (method A); R_f 0.6, $CHCl_3$−AcOEt (9:1).

(*S*)-1-(4-Methoxybenzyl)-4-acetyl-3,4-dihydro-3-methylthieno[3,2-*e*][1,4]diazepine-2,5-dione (9): yield 20%; beige solid, mp 67−70 °C; $[\alpha]^{20}_D$ −46.7 (*c* 0.2, DMSO); ^1H NMR (DMSO-d_6) δ 8.03 (d, 1H, J = 5.4 Hz), 7.13 (d, 1H, J = 5.4 Hz), 7.09 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.5 Hz), 5.88 (quad, 1H, J = 7.6 Hz), 5.15 (d, 1H, J = 15.9 Hz), 5.03 (d, 1H, J = 15.9 Hz), 3.71 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.3, 168.6, 163.6, 158.4, 141.0, 135.4, 128.4, 127.7, 123.1, 114.1, 113.9, 55.0, 51.0, 49.1, 26.1, 13.9; HRMS calcd for $[M + H^+]$ $C_{18}H_{19}N_2O_4S$ 359.1066, found 359.1045; R_t 2.66 (method A); R_f 0.6, $CHCl_3$−AcOEt (9:1).

Typical Procedure for the *N*(4)-Boc Protection of Diazepinediones 2−5. A solution of thienodiazepinedione **3** (4.00 g, 13.2 mmol) in THF (100 mL) was treated with NaH (60% dispersed in oil, 1.33 g, 33.1 mmol) at 0 °C and stirred for 5 min. Then Boc_2O (5.75 g, 26.4 mmol) was added and the reaction mixture was left to stir to rt for 1 h. The volatile material was evaporated and the residue was partitioned between H_2O and EtOAc. The aqueous

phase was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was further purified by flash chromatography.

***tert*-Butyl 2,3-dihydro-1-methyl-2,5-dioxo-1*H*-thieno[3,2-*e*]-[1,4]diazepine-4(5*H*)-carboxylate (10):** yield 83%; off-white solid, mp 148−149 °C; ^{1}H NMR (DMSO-d_6) δ 8.06 (d, 1H, J = 5.5 Hz), 7.26 (d, 1H, J = 5.5 Hz), 4.43 (br s, 2H), 3.34 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 167.3, 160.9, 150.6, 143.0, 134.2, 122.8, 109.1, 83.2, 47.8, 33.9, 27.5; HRMS calcd for [M + H$^+$] $C_{13}H_{17}N_2O_4S$ 297.0909, found 297.0910; R_t 1.99 (method A); R_f 0.5, $CHCl_3$−AcOEt (4:1).

***tert*-Butyl 1-(4-methoxybenzyl)-2,3-dihydro-2,5-dioxo-1*H*-thieno[3,2-*e*][1,4]diazepine-4(5*H*)-carboxylate (11):** yield 94%; light beige solid, mp 140−142 °C; ^{1}H NMR (DMSO-d_6) δ 7.98 (d, 1H, J = 5.4 Hz), 7.20 (d, 1H, J = 5.4 Hz), 7.09 (d, 2H, J = 7.2 Hz), 6.85 (d, 2H, J = 7.0 Hz), 5.09 (s, 2H), 4.54 (s, 2H), 3.70 (s, 3H), 3.30 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 167.1, 160.8, 158.4, 150.5, 141.8, 134.2, 128.5, 127.9, 123.9, 123.0, 114.0, 83.3, 55.0, 48.1, 48.0, 27.5; HRMS calcd for [M + H$^+$] $C_{20}H_{23}N_2O_5S$ 403.1328, found 403.1301; R_t 2.74 (method A); R_f 0.5, $CHCl_3$−AcOEt (9:1).

(*S*)-*tert*-Butyl 1-(4-methoxybenzyl)-3-benzyl-2,3-dihydro-2,5-dioxo-1*H*-thieno[3,2-*e*][1,4]diazepine-4(5*H*)-carboxylate (12): yield 48%; yellow beige solid, mp 66−68 °C dec; $[\alpha]^{20}_D$ −13.3 (*c* 0.2, DMSO); ^{1}H NMR (DMSO-d_6 at 65 °C) δ 8.02 (br s, 1H), 7.27 (m, 5H), 7.06 (d, 3H, J = 8.5 Hz), 6.83 (d, 2H, J = 7.8 Hz), 5.55 (br s, 1H), 5.09 (br s, 2H), 3.72 (s, 3H), 3.33 (br s, 0.5H), 2.86 (m, 1.5H), 1.42 (s, 9H); ^{1}H NMR (DMSO-d_6 at 20 °C) δ 8.09 (d, 0.7H, J = 5.4 Hz), 7.98 (d, 0.3H, J = 5.4 Hz), 7.27 (m, 4.6H), 7.04 (m, 3.3H), 6.85 (d, 1.3H, J = 8.6 Hz), 6.78 (d, 0.7H, J = 8.5 Hz), 5.55 (t, 0.7H, J = 8.7 Hz), 5.45 (d, 0.3H, J = 15.7 Hz), 5.09 (t, 1.3H, J = 17.1 Hz), 4.93 (d, 0.3H, J = 15.6 Hz), 4.78 (t, 0.3H, J = 7.5 Hz), 3.71 (s, 2H), 3.68 (s, 1H), 3.55 (dd, 0.3H, J = 13.7, 8.2 Hz), 3.40 (dd, 0.3H, J = 13.9, 7.0 Hz), 3.00 (dd, 0.7H, J = 13.8, 7.9 Hz), 2.82 (dd, 0.7H, J = 13.8, 9.7 Hz), 1.44 (s, 3H), 1.37 (s, 6H); HRMS calcd for [M + H$^+$] $C_{27}H_{29}N_2O_5S$ 493.1797, found 493.1772; R_t 3.32 (method A); R_f 0.9, $CHCl_3$−AcOEt (9:1).

(*S*)-*tert*-Butyl 1-(4-methoxybenzyl)-2,3-dihydro-3-methyl-2,5-dioxothieno[3,2-*e*][1,4]diazepine-4(5*H*)-carboxylate (13): yield 45%; orange solid, mp 147−150 °C; ^{1}H NMR (DMSO-d_6) δ 7.99 (d, 1H, J = 5.3 Hz), 7.25 (br s, 1H), 7.07 (d, 2H, J = 8.3 Hz), 6.84 (d, 2H, J = 8.0 Hz), 5.20 (br s, 2H), 3.71 (m, 1H), 3.70 (s, 3H), 3.30 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 169.1, 158.9, 159.0, 142.1, 135.0, 129.0, 128.3, 124.2, 123.6, 114.4, 113.8, 83.8, 55.4, 49.0, 49.0, 27.9, 14.5; HRMS calcd for [M + H$^+$] $C_{21}H_{25}N_2O_5S$ 417.1484, found 417.1470; R_t 2.90 (method A); R_f 0.7, $CHCl_3$−AcOEt (9:1).

Typical Procedure for the Synthesis of Ketones 14 or 18. A solution of *N*-Boc thienodiazepinedione **11** (0.200 g, 0.5 mmol) in dry THF (15 mL) was treated with a commercially available 1.0 M solution of PhMgBr (0.6 mL, 0.6 mmol) in THF then the solution was stirred for 5 min at rt. The volatile material was evaporated and the residue was purified by flash chromatography.

Ketone 14a: yield 66%; beige solid, mp 46−50 °C; ^{1}H NMR (DMSO-d_6) δ 7.98 (d, 1H, J = 4.7 Hz), 7.63 (m, 5H), 7.04 (d, 1H, J = 4.7 Hz), 6.98 (d, 2H, J = 7.7 Hz), 6.86 (t, 1H, J = 5.4 Hz), 6.69 (d, 2H, J = 7.8 Hz), 4.68-.53 (m, 2H), 3.69 (m, 2H), 3.67 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 186.8, 168.7, 158.5, 155.6, 142.55, 138.2, 133.8, 132.7, 132.1, 129.8, 129.2, 128.8, 128.6, 128.3, 113.5, 77.9, 54.8, 51.2, 42.6, 28.2; HRMS calcd for [M + H$^+$] $C_{26}H_{29}N_2O_5S$ 481.1797, found 481.1782; R_t 3.16 (method A); R_f 0.7, $CHCl_3$−AcOEt (7:1).

Typical Direct Procedure for the Synthesis of 1-(4-methoxybenzyl)-5-aryl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (16). A solution of Boc-protected thienodiazepinedione **11** (0.200 g, 0.5 mmol) in dry THF (15 mL) was treated with a commercially available 1.0 M solution of PhMgBr (0.6 mL, 0.6 mmol) in THF then the mixture was stirred for 5 min at rt. Volatile material were evaporated and the ketone **14a** was dissolved in a TFA−DCM (1:1) solution (15 mL) and stirred for 15 min at rt. To the stirring solution of amine **15a** is added triethylamine dropwise until pH 8 then the solution is stirred for 5 min. The volatile material was evaporated and the residue was partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residual thienodiazepine **16** was further purified by flash column chromatography.

1-(4-Methoxybenzyl)-5-phenyl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (16a): yield 58%; beige solid, mp 45−48 °C; ^{1}H NMR (DMSO-d_6) δ 7.87 (d, 1H, J = 5.4 Hz), 7.51-7.41 (m, 5H), 7.36 (d, 1H, J = 5.4 Hz), 6.99 (d, 2H, J = 8.5 Hz), 6.78 (d, 2H, J = 8.5 Hz), 5.09 (s, 2H), 4.37 (s, 2H), 3.67 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.5, 164.4, 158.4, 144.6, 138.6, 130.7, 130.3, 128.9, 128.8, 128.2, 128.0, 125.1, 122.1, 113.8, 58.0, 55.0, 48.2; HRMS calcd for [M + H$^+$] $C_{21}H_{19}N_2O_2S$ 363.1167, found 363.1177; R_t 2.11 (method A).

1-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (16b): yield 62%; light-beige solid, mp 58−61 °C; ^{1}H NMR (DMSO-d_6) δ 7.91 (d, 1H, J = 5.4 Hz), 7.50 (d, 2H, J = 8.8 Hz), 7.36 (d, 1H, J = 5.4 Hz), 7.01 (d, 2H, J = 8.8 Hz), 6.99 (d, 2H, J = 8.6 Hz), 6.78 (d, 2H, J = 8.7 Hz), 5.08 (s, 2H), 4.34 (br s, 2H), 3.81 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.6, 164.0, 161.7, 158.3, 145.1, 131.3, 131.0, 130.2, 128.7, 128.0, 124.8, 122.3, 113.8, 113.7, 57.0, 55.4, 55.0, 48.4; HRMS calcd for [M + H$^+$] $C_{22}H_{21}N_2O_3S$ 393.1273, found 393.1263; R_t 2.19 (method A); R_f 0.4, $CHCl_3$−AcOEt (7:3).

1-(4-Methoxybenzyl)-5-(4-chlorophenyl)-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (16c): yield 66%; light-beige solid, mp 56−59 °C; ^{1}H NMR (DMSO-d_6) δ 7.91 (d, 1H, J = 5.4 Hz), 7.53 (s, 4H), 7.36 (d, 1H, J = 5.4 Hz), 6.99 (d, 2H, J = 8.6 Hz), 6.79 (d, 2H, J = 8.7 Hz), 5.09 (s, 2H), 4.37 (br s, 2H), 3.68 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.3, 163.5, 158.4, 145.2, 136.9, 135.8, 131.2, 130.8, 128.7, 128.4, 128.0, 124.3, 122.3, 113.9, 57.7, 55.0, 48.4; HRMS calcd for [M + H$^+$] $C_{21}H_{18}N_2O_2SCl$ 397.0778, found 397.0760; R_t 2.33 (method A); R_f 0.6, $CHCl_3$−AcOEt (7:3).

(*S*)-1-(4-Methoxybenzyl)-3-benzyl-5-phenyl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (16d): yield 99%; light yellow solid, mp 68−70 °C; $[\alpha]^{20}_D$ 2.0 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6) δ 7.85 (d, 1H, J = 5.4 Hz), 7.51−7.20 (m, 11H), 6.93 (d, 2H, J = 8.5 Hz), 6.74 (d, 2H, J = 8.5 Hz), 5.34 (d, 1H, J = 15.3 Hz), 4.87 (d, 1H, J = 15.3 Hz), 3.92 (t, 1H, J = 6.8 Hz), 3.67 (s, 3H), 3.57-3.40 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 165.9, 162.4, 158.4, 144.3, 139.1, 138.3, 130.7, 130.5, 129.7, 128.9, 128.8, 128.2, 128.1, 128.0, 126.0, 125.3, 122.2, 113.8, 66.0, 55.0, 48.6, 37.8; HRMS calcd for [M + H$^+$] $C_{28}H_{25}N_2O_2S$ 453.1637, found 453.1637; R_t 2.76 (method A); R_f 0.7, $CHCl_3$−AcOEt (9:1).

(*S*)-1-(4-Methoxybenzyl)-3-benzyl-5-(4-methoxyphenyl)-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (16e): yield 99%; yellow solid, mp 70−72 °C; $[\alpha]^{20}_D$ −7.9 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6) δ 7.83 (d, 1H, J = 5.4 Hz), 7.39−7.16 (m, 8H), 6.97 (d, 2H, J = 8.7 Hz), 6.92 (d, 2H, J = 8.5 Hz), 6.74 (d, 2H, J = 8.4 Hz), 5.32 (d, 1H, J = 15.4 Hz), 4.87 (d, 1H, J = 15.3 Hz), 3.87 (t, 1H, J = 6.6 Hz), 3.79 (s, 3H), 3.67 (s, 3H), 3.51−3.40 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.2, 161.5, 161.3, 158.3, 144.1, 139.2, 139.2, 130.6, 130.2, 129.7, 128.8, 128.0, 128.0, 126.0, 125.5, 122.2, 113.8, 113.6, 66.0, 55.3, 55.0, 48.6, 37.8; HRMS calcd for [M + H$^+$] $C_{29}H_{27}N_2O_3S$ 483.1742, found 483.1761; R_t 2.73 (method A); R_f 0.6, $CHCl_3$−AcOEt (9:1).

(*S*)-1-(4-Methoxybenzyl)-3-benzyl-5-(4-chlorophenyl)-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (16f): yield 99%; light yellow solid, mp 61−64 °C; $[\alpha]^{20}_D$ −3.4 (*c* 0.2, DMSO); ^{1}H NMR ($CDCl_3$) δ 7.47−7.31 (m, 10H), 7.00 (d, 1H, J = 5.4 Hz), 6.97 (d, 2H, J = 8.7 Hz), 6.72 (d, 2H, J = 8.7 Hz), 5.30 (d, 1H, J = 15.2 Hz), 4.85 (d, 1H, J = 15.2 Hz), 3.96 (t, 1H, J = 6.7 Hz), 3.74 (s, 3H), 3.80−3.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.5, 162.8, 159.1, 145.3, 139.2, 137.7, 136.5, 131.3, 130.4, 130.1, 129.4, 128.7, 128.5, 128.5, 128.4, 126.4, 121.7, 114.2, 66.6, 55.4, 50.4, 38.1; HRMS

calcd for $[M + H^+]$ $C_{28}H_{24}N_2O_2SCl$ 487.1247, found 487.1245; R_t 3.19 (method A); R_f 0.6, $CHCl_3$−AcOEt (95:5).

(*S*)-1-(4-Methoxybenzyl)-3-methyl-5-phenyl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (16g): yield 86%; white solid, mp 58−60 °C; $[\alpha]^{20}_D$ 56.2 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6) δ 7.86 (d, 1H, J = 5.4 Hz), 7.51−7.47 (m, 5H), 7.38 (d, 1H, J = 5.4 Hz), 6.95 (d, 2H, J = 8.3 Hz), 6.76 (d, 2H, J = 8.4 Hz), 5.35 (d, 1H, J = 15.3 Hz), 4.86 (d, 1H, J = 15.2 Hz), 3.87 (quad, 1H, J = 6.3 Hz), 3.67 (s, 3H), 1.64 (d, 3H, J = 6.3 Hz); ^{13}C NMR (DMSO-d_6) δ 167.1, 162.1, 158.3, 144.2, 138.4, 130.6, 130.2, 128.9, 128.2, 128.1, 125.5, 122.1, 113.8, 109.1, 59.7, 55.0, 48.5, 18.1; HRMS calcd for $[M + H^+]$ $C_{22}H_{21}N_2O_2S$ 377.1324, found 377.1308; R_t 2.14 (method A); R_f 0.4, $CHCl_3$−AcOEt (9:1).

(*S*)-1-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-3-methyl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (16h): yield 71%; white solid, mp 46−50 °C; $[\alpha]^{20}_D$ 21.3 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6) δ 7.83 (d, 1H, J = 5.4 Hz), 7.45 (d, 2H, J = 8.5 Hz), 7.35 (d, 1H, J = 5.3 Hz), 6.98 (d, 2H, J = 8.8 Hz), 6.94 (d, 2H, J = 8.9 Hz), 6.75 (d, 2H, J = 8.2 Hz), 5.32 (d, 1H, J = 15.4 Hz), 4.86 (d, 1H, J = 15.4 Hz), 3.83 (quad, 1H, J = 6.3 Hz), 3.80 (s, 3H), 3.67 (s, 3H), 1.62 (d, 3H, J = 6.3 Hz); ^{13}C NMR (DMSO-d_6) δ 167.4, 161.3, 161.2, 158.3, 144.1, 130.8, 130.5, 130.0, 128.9, 128.0, 125.7, 122.1, 113.8, 113.5, 59.4, 55.3, 55.0, 48.5, 18.1; HRMS calcd for $[M + H^+]$ $C_{23}H_{23}N_2O_3S$ 407.1429, found 407.1404; R_t 2.23 (method A); R_f 0.5, $CHCl_3$−AcOEt (9:1).

Typical PMB Removal Procedure for the Synthesis of 5-Aryl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (17). A solution of 1-(4-methoxybenzyl)-5-phenyl-thienodiazepinone **16a** (0.100 g, 0.28 mmol) in 6 mL of CH_3CN-H_2O (3:1) was treated with CAN (0.757 g, 1.38 mmol) and the mixture was stirred for 2 h at rt. Volatile material was lyophilized and the residue was partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. Trituration with a solution of Et_2O−pentane (1:1) afforded pure products **17**.

5-Phenyl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (17a): yield 54%; white solid, mp 56−58 °C; ^{1}H NMR (DMSO-d_6) δ 11.0 (br s, 1H), 7.88 (d, 1H, J = 5.3 Hz), 7.63−7.43 (m, 5H), 6.95 (d, 1H, J = 5.3 Hz), 4.23 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 167.0, 164.2, 142.7, 139.2, 130.9, 130.5, 129.2, 128.1, 121.5, 109.0, 58.4; HRMS calcd for $[M + H^+]$ $C_{13}H_{11}N_2O_1S$ 243.0592, found 243.0609; R_t 1.27 (method A).

5-(4-Methoxyphenyl)-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (17b): yield 60%; light-yellow solid, mp 71 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.50 (br s, 1H), 8.15 (d, 1H, J = 5.3 Hz), 7.69 (d, 2H, J = 8.7 Hz), 7.08 (d, 2H, J = 8.7 Hz), 7.05 (d, 1H, J = 5.3 Hz), 4.26 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.5, 165.2, 162.6, 145.0, 136.0, 132.4, 128.1, 122.2, 119.8, 114.0, 55.6, 55.2; HRMS calcd for $[M + H^+]$ $C_{14}H_{13}N_2O_2S$ 273.0698, found 273.0676; R_t 1.48 (method A).

5-(4-Chlorophenyl)-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (17c): yield 52%; white solid, mp 201−204 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.69 (s, 1H), 8.24 (d, 1H, J = 5.1 Hz) 7.76 (d, 2H, J = 8.2 Hz), 7.64 (d, 2H, J = 8.2 Hz), 7.08 (d, 1H, J = 5.2 Hz), 4.33 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 167.8, 165.5, 146.0, 137.7, 137.6, 134.1, 132.3, 128.7, 122.2, 119.0, 55.0; HRMS calcd for $[M + H^+]$ $C_{13}H_{10}N_2OSCl$ 277.0202, found 277.0210; R_t 1.55 (method A).

(*S*)-3-Benzyl-5-phenyl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (17d): yield 79%; off-white solid, mp 94−96 °C dec; $[\alpha]^{20}_D$ −14.8 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6) δ 11.46 (s, 1H), 8.08 (s, 1H), 7.54 (m, 5H), 7.31 (m, 5H), 6.79 (s, 1H), 3.96 (s, 1H), 3.42 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.4, 163.9, 144.4, 138.5, 136.7, 135.0, 131.8, 130.0, 129.6, 128.4, 128.1, 126.2, 121.8, 120.5, 64.8, 36.0; HRMS calcd for $[M + H^+]$ $C_{20}H_{17}N_2OS$ 333.1062, found 333.1041; R_t 2.02 (method A); R_f 0.4, $CHCl_3$−AcOEt (4:1).

(*S*)-3-Benzyl-5-(4-methoxyphenyl)-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (17e): yield 85%; off-white solid, mp 89−91 °C dec; $[\alpha]^{20}_D$ −35.3 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6) δ 11.65 (s, 1H), 8.21 (br s, 1H), 7.53 (d, 2H, J = 8.8 Hz), 7.40 (d, 2H, J = 7.2 Hz), 7.32 (t, 2H, J = 7.4 Hz), 7.23 (t, 1H, J = 7.1 Hz), 7.08 (d, 2H, J = 9.0 Hz), 7.07 (d, 1H, J = 4.9 Hz), 4.03 (m, 1H), 3.85 (s, 3H), 3.52−3.34 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.5, 163.9, 162.9, 145.3, 138.0, 137.0, 132.6, 131.3, 129.6, 128.2, 126.4, 122.1, 120.0, 114.0, 63.6, 55.6, 35.1; HRMS calcd for $[M + H^+]$ $C_{21}H_{19}N_2O_2S$ 363.1167, found 363.1141; R_t 2.17 (method A).

(*S*)-3-Benzyl-5-(4-chlorophenyl)-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (17f): yield 89%; off-white solid, mp 88−90 °C dec; $[\alpha]^{20}_D$ −10.3 (*c* 0.2, DMSO); ^{1}H NMR (DMSO-d_6) δ 11.41 (s, 1H), 8.05 (d, 1H, J = 5.1 Hz), 7.56 (s, 4H), 7.38 (d, 2H, J = 7.0 Hz), 7.30 (t, 2H, J = 7.3 Hz), 7.22 (t, 1H, J = 7.2 Hz), 6.99 (d, 1H, J = 5.3 Hz), 3.89 (m, 1H), 3.48 (dd, 1H, J = 13.7, 5.5 Hz), 3.38 (dd, 1H, J = 13.7, 8.6 Hz); ^{13}C NMR (DMSO-d_6) δ 166.4, 162.3, 144.0, 138.7, 136.4, 136.0, 134.1, 131.5, 129.6, 128.5, 128.1, 126.1, 121.7, 120.3, 65.2, 36.4; HRMS calcd for $[M + H^+]$ $C_{20}H_{16}N_2OSCl$ 367.0672, found 367.0663; R_t 2.33 (method A).

(S)-3-Methyl-5-phenyl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (17g): yield 75%; white solid, ^{1}H NMR (DMSO-d_6) δ 11.52 (br s, 1H), 8.15 (s, 1H), 7.73−7.38 (m, 5H), 7.04 (d, 1H, J = 5.4 Hz), 3.87 (quad, 1H, J = 6.3 Hz), 1.64 (d, 3H, J = 6.3 Hz); HRMS: calcd for $[M + H^+]$ $C_{14}H_{13}N_2OS$ 257.0749, found 257.0757; R_t 1.30 (method A).

(*S*)-5-(4-Methoxyphenyl)-3-methyl-1*H*-thieno[3,2-*e*][1,4]diazepin-2(3*H*)-one (17h): yield 80%; white solid, mp 189−191 °C; $[\alpha]^{20}_D$ −135.6 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6) δ 11.90 (s, 1H), 8.37 (d, 1H, J = 5.4 Hz), 7.77 (d, 2H, J = 8.6 Hz), 7.17 (d, 2H, J = 8.9 Hz), 7.15 (d, 1H, J = 5.4 Hz), 4.07 (quad, 1H, J = 5.7 Hz), 3.89 (s, 3H), 1.63 (d, 3H, J = 6.0 Hz); ^{13}C NMR (DMSO-d_6) δ 167.2, 165.3, 163.7, 146.8, 133.8, 125.5, 122.3, 118.9, 114.2, 114.2, 56.9, 55.8, 14.3; HRMS calcd for $[M + H^+]$ $C_{15}H_{15}N_2O_2S$ 287.0854, found 287.0825; R_t 1.52 (method A).

Typical Direct Procedure for the Synthesis of 6-Aminothieno[3,2-*b*]pyridinones (20). A solution of Boc-protected *N*-methylthienodiazepinedione **14a** (1.200 g, 3.0 mmol) in dry THF (100 mL) was treated with a commercially available 1.0 M solution of *p*-methoxyphenylmagnesium bromide (3.3 mL, 3.3 mmol) in THF then the mixture was stirred for 5 min at rt. Complete conversion of starting material was ascertained by LCMS or TLC. The yellow solution was then treated with a commercially available 1.0 M solution of KO*t*Bu (6.6 mL, 6.6 mmol) in THF and stirred for 30 min at rt. *p*-Toluenesulphonic acid (2.500 g, 13.2 mmol) was added to the cloudy solution and then the solution was stirred at rt for 10 min. Volatile material was evaporated and the residue was partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residual **20b** was further purified by flash column chromatography.

***tert*-Butyl 4-(4-methoxybenzyl)-7-(4-chlorophenyl)-4,5,6,7-tetrahydro-7-hydroxy-5-oxothieno[3,2-*b*]pyridin-6-ylcarbamate (19c):** light yellow solid, mp 55 °C; ^{1}H NMR (DMSO-d_6) δ 8.01 (d, 1H, J = 5.1 Hz), 7.61 (d, 2H, J = 8.5 Hz), 7.56 (d, 2H, J = 8.5 Hz), 7.08 (d, 1H, J = 5.1 Hz), 6.95 (s, 1H), 6. 94 (d, 2H, J = 8.1 Hz), 6.65 (d, 2H, J = 8.4 Hz), 4.57 (d, 2H, J = 6.2 Hz), 3.60 (m, 5H), 1.38 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 185.7, 168.8, 158.5, 155.7, 142.5, 137.7, 136.7, 133.6, 132.4, 130.8, 129.9, 129.3, 128.5, 128.1, 113.5, 78.0, 54.8, 51.3, 42.7, 28.2; HRMS calcd for $[M + H^+]$ $C_{26}H_{28}N_2O_5SCl$ 515.1407, found 515.1379; R_t 3.29 (method A); R_f 0.4, DCM−AcOEt (9:1).

***tert*-Butyl 4-(4-methoxybenzyl)-4,5-dihydro-5-oxo-7-phenylthieno[3,2-*b*]pyridin-6-ylcarbamate (20a):** yield 52%; beige solid, mp 198−200 °C; ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 1H), 7.91 (d, 1H, J = 5.5 Hz), 7.50 (m, 5H), 7.43 (d, 1H, J = 5.5 Hz), 7.32 (d, 2H, J = 8.6 Hz), 6.90 (d, 2H, J = 8.7 Hz), 5.43 (s, 2H), 3.73 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 159.8, 158.6, 154.1, 140.8, 135.6, 131.0, 129.4, 128.9, 128.4, 128.0, 121.8, 118.5, 118.0, 114.0, 78.3, 55.1, 47.3, 27.9; HRMS calcd for $[M + H^+]$ $C_{26}H_{27}N_2O_4S$ 463.1692, found 463.1692; R_t 3.03 (method A); R_f 0.5, DCM−AcOEt (4:1).

***tert*-Butyl 4-(4-methoxybenzyl)-4,5-dihydro-7-(4-methoxyphenyl)-5-oxothieno[3,2-*b*]pyridin-6-ylcarbamate (20b):** yield 47%; beige solid, mp 154−157 °C; ^{1}H NMR (DMSO-d_6) δ 7.96 (br s, 1H), 7.88 (d, 1H, J = 5.5 Hz), 7.44 (d, 2H, J = 8.4 Hz), 7.39 (d, 1H, J = 5.6 Hz), 7.31 (d, 2H, J = 8.4 Hz), 7.06 (d, 2H, J = 8.5 Hz), 6.89 (d, 2H, J = 8.5 Hz), 5.41 (s, 2H), 3.81 (s, 3H), 3.71 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 159.8, 159.6, 158.6, 154.2, 140.7, 131.5, 130.8, 129.8, 129.4, 128.8, 127.7, 121.6, 118.8, 117.9, 113.9, 113.8, 113.7, 78.2, 55.2, 55.0, 47.3, 28.0; HRMS calcd for [M + H$^+$] $C_{27}H_{29}N_2O_5S$ 493.1797, found 493.1779; R_t 3.07 (method A); R_f 0.7, DCM−AcOEt (7:3).

***tert*-Butyl 4,5-dihydro-4-methyl-5-oxo-7-phenylthieno[3,2-*b*]pyridin-6-ylcarbamate (20d):** yield 51%; off-white solid, mp 77−79 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (m, 3H), 7.51 (d, 1H, J = 5.5 Hz), 7.43 (m, 2H), 7.10 (d, 1H, J = 5.5 Hz), 6.64 (br s, 1H), 3.80 (s, 3H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 160.1, 152.7, 140.0, 138.5, 136.7, 130.0, 129.0, 128.7, 128.7, 128.0, 121.8, 116.5, 80.3, 32.9, 28.0; HRMS calcd for [M + H$^+$] $C_{19}H_{21}N_2O_3S$ 357.1273, found 357.1259; R_t 2.66 (method A); R_f 0.4, $CHCl_3$−AcOEt (1:1).

***tert*-Butyl 4,5-dihydro-7-(4-methoxyphenyl)-4-methyl-5-oxothieno[3,2-*b*]pyridin-6-ylcarbamate (20e):** yield 49%; beige solid, mp 81−82 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 2H, J = 8.8 Hz), 7.51 (d, 1H, J = 5.4 Hz), 7.09 (d, 1H, J = 5.4 Hz), 6.99 (d, 2H, J = 8.7 Hz), 6.61 (br s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 160.1, 160.0, 152.9, 140.0, 138.8, 132.2, 129.4, 129.1, 128.9, 121.7, 116.5, 114.2, 80.2, 55.5, 32.9, 28.1; HRMS calcd for [M + H$^+$] $C_{20}H_{23}N_2O_4S$ 387.1379, found 387.1378; R_t 2.63 (method A); R_f 0.3, $CHCl_3$−AcOEt (1:1).

***tert*-Butyl 7-(4-chlorophenyl)-4,5-dihydro-4-methyl-5-oxothieno[3,2-*b*]pyridin-6-ylcarbamate (20f):** yield 55%; beige solid, mp 120−121 °C; ^{1}H NMR (DMSO-d_6) δ 8.07 (br s, 1H), 7.97 (d, 1H, J = 5.5 Hz), 7.59 (d, 2H, J = 5.4 Hz), 7.48 (d, 2H, J = 8.5 Hz), 7.44 (d, 1H, J = 5.6 Hz), 3.70 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 159.5, 153.8, 141.5, 134.5, 133.5, 130.8, 129.8, 128.5, 121.6, 117.8, 117.6, 78.4, 32.4, 27.8; HRMS calcd for [M + H$^+$] $C_{19}H_{20}N_2O_3SCl$ 391.0883, found 391.0869; R_t 2.93 (method A); R_f 0.4, $CHCl_3$−AcOEt (1:1).

Procedure for the Synthesis of 6-(Oxothieno[3,2-*b*]pyridinyl)-ureas (22). A solution of thienopyridinone **20b** (0.100 g, 0.2 mmol) in TFA−DCM (1:1) was stirred for 30 min at rt. Complete conversion of starting material was ascertained by LCMS or TLC. The reddish solution was then evaporated as best as possible (and re-evaporated after addition of Et_2O). The residue was dissolved in DCM, treated with the corresponding isocyanate (0.2 mmol), and stirred for 10 min at rt. Volatile material was evaporated and the residue was filtered over a frit, washed with H_2O and CH_3CN, and dried under vacuum overnight to afford pure 1-(4-(4-methoxybenzyl)-4,5-dihydro-7-(4-methoxyphenyl)-5-oxothieno[3,2-*b*]pyridin-6-yl)-3-(4-chlorophenyl)urea (**22**): yield 62%; gray solid, mp 186−188 °C; ^{1}H NMR (DMSO-d_6) δ 8.95 (s, 1H), 7.90 (d, 1H, J = 5.5 Hz), 7.65 (s, 1H), 7.49 (d, 2H, J = 8.6 Hz), 7.44 (d, 1H, J = 5.6 Hz), 7.37 (d, 2H, J = 8.6 Hz), 7.34 (d, 2H, J = 8.6 Hz), 7.26 (d, 2H, J = 8.8 Hz), 7.05 (d, 2H, J = 8.6 Hz), 6.90 (d, 2H, J = 8.5 Hz), 5.44 (s, 2H), 3.79 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 159.8, 159.4, 158.6, 153.3, 141.0, 140.0, 139.0, 130.3, 129.3, 128.9, 128.8, 128.4, 128.1, 124.9, 121.6, 119.5, 119.3, 117.9, 113.9, 113.8, 55.1, 55.0, 47.4; HRMS calcd for [M + H$^+$] $C_{29}H_{25}N_3O_4SCl$ 546.1254, found 546.1225; R_t 2.99 (method A).

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectral data for compounds **6**−**13**, **14a**, **16**, **17**, **19c**, **20**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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