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Dihydro-3-(triphenylphosphoranylidene)-2,5-thiophendione: a convenient synthon for the preparation of substituted 1,4-thiazepin-5-ones and piperidinones via the intermediacy of thioacids

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ABSTRACT

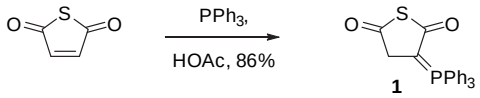
Reaction of thiomaleic anhydride with triphenylphosphine gives the title compound, which undergoes reaction with a variety of aldehydes to give a range of alkylidene thiomaleic anhydrides (substituted monothioitaconic anhydrides). Subsequent treatment with *tert*-butoxycarbonylamino-substituted thiols, or under radical conditions with *tert*-butoxycarbonylamino-substituted alkyl halides results in a series of substituted monothiomaleic anhydrides, that on exposure to trifluoroacetic acid and then base lead to thiocarboxyl substituted 1,4-thiazepin-5-ones and piperidinones, respectively, that are ultimately trapped by reaction with 2,4-dinitrobenzenesulfonamides to give the corresponding amides.

1. Introduction

Monothioacids[1–6] present numerous advantages over the simple carboxylic acids by virtue of their acidity and the enhanced nucleophilicity of the thiocarboxylate function. Thus, for example, thioacids may be alkylated selectively in the presence of acids,[7] and react with electrophiles such as electron-deficient aromatic and heteroaromatic systems,[8–11] isothiocyanates, and isocyanates,[12,13] isonitriles,[14–17] a variety of coupling reagents,[18–21] azides,[22–30] and alkenes[31–34] more efficiently and under milder conditions than the corresponding acids. In this context we[35,36] and others[37] have been exploring new methods for the preparation of a variety of thioacids for subsequent application in amide and peptide bond formation. In particular we have been interested in methods based on the nucleophilic ring opening of monothio thiosuccinic and thiomaleic anhydrides,[38–42] and of monothio-β-lactones[43] and on the application of the ensuing thioacids in multicomponent coupling processes. Here, we report on the preparation of dihydro-3-(triphenylphosphoranylidene)-2,5-thiophendione, its elaboration to a variety of monothioitaconic anhydride derivatives, and the use of these latter products in multicomponent coupling reactions leading to the formation of 1,4-thiazepin5-ones.

2. Results and discussion

By analogy with the chemistry of 2-(triphenylphosphanylidene-succinic anhydride),[44–51] we reasoned that treatment of monothiomaleic anhydride[39,40,52,53] with triphenylphosphine would result in the formation of dihydro-3-(triphenylphosphoranylidene)-2,5-thiophendione **1**, and that this ylide would be stable, isolable, and a suitable partner for reaction with aldehydes to give substituted monothioitaconic anhydride derivatives. In the event, reaction of monothiomaleic anhydride with triphenylphosphine in glacial acetic acid at room temperature provided the crystalline **1** in 86% yield (Scheme 1).



Scheme 1. Formation of dihydro-3-(triphenylphosphoranylidene)-2,5-thiophendione.

Subsequent reaction with a selection of aromatic and aliphatic aldehydes at room temperature gave the corresponding substituted monothioitaconic anhydrides in excellent yields as the pure *E*-isomers (Table 1), as ascertained by NOE studies, in agreement with the comparable reactions[46] of 2-(triphenylphosphanylidene)succinic anhydride.

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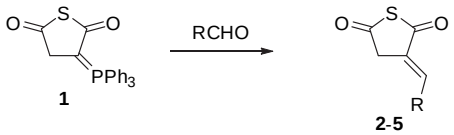
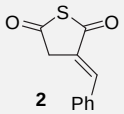
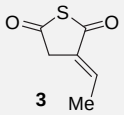
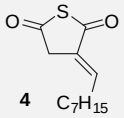
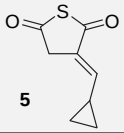
Table 1
Olefination reactions of reagent **1**



Entry	RCHO	Product	% Yield
1	PhCHO	 **2**	78
2	MeCHO	 **3**	76
3	$C_7H_{15}CHO$	 **4**	72
4	*c*-C_3H_5CHO	 **5**	84

With a series of alkylidene monothiosuccinic anhydrides in hand, we turned our attention to tandem Michael addition–nucleophilic ring opening processes with suitably constituted mercaptoamines, of the kind previously practiced on monothiomaleic anhydride,[39,40] with subsequent trapping of the released thioacid by reaction with 2,4-dinitrobenzenesulfonamides.[9–11,36] A series of reactions were conducted in which either 2-mercaptoaniline or 2-mercaptoethylamine were stirred in DMF at 0 °C overnight with the alkylidene thiosuccinic anhydride before the addition of cesium carbonate and a 2,4-dinitrobenzenesulfonamide leading, ultimately, to the isolation of a series of substituted 1,4-thiazepin-5-ones, or their benzo-fused analogs, as presented in Table 2.

For each of the tandem sequences reported in Table 2 only the thiazepinone regioisomer, arising from ring closure of the amine onto the proximal carbonyl group following conjugate addition, was isolated.[54] In the case of the ethylidene succinic anhydride (Table 2, entries 5–8), two diastereomeric products were formed in an approximate equimolar ratio and no attempt was made to separate the two isomers. With moderately more bulky octylidene and cyclopropylidene systems **4** and **5** (Table 2, entries 9–12), low to moderate selectivity was observed in favor of the *trans*-isomer, whereas in the case of the somewhat more hindered benzylidene system **2** the *trans*-isomer was typically favored by a factor of 4–5:1 over the *cis*-isomer (Table 2, entries 1–4). This preferential formation of the *trans*-isomers, with selectivity increasing with the size of the olefinic substituent, is best rationalized in terms the standard models for stereoselective protonation of enolates bearing a stereogenic center β-to the incipient carbonyl group.[55–64] Thus, following conjugate addition of the thiolate anion, the enolate adopts a conformation that minimizes $A^{1,3}$ strain[65,66] leading to protonation through either of transitions states **A** or **B** (Scheme 2). As the size of the alkene substitutent (*R*) increases transition state **B** is increasingly favored, resulting in overall increased *trans*-selectivity.[67]

Having demonstrated the 1,4-addition sequence with aminothiols, we turned our attention to the conjugate addition of functionalized carbon radicals and the preparation of piperidinone-based systems. Thus, radical addition of *N*-(*tert*-butoxycarbonyl) 2-iodoethylamine **22** to the ethylidene succinic anhydride **3** in toluene at 80 °C under the aegis of tris(trimethylsilyl)silane (TTMS)[68] and azobisisobutyronitrile (AIBN), gave the adduct **23** in 52% yields as a 3:1 *anti*/*syn* mixture of diastereoisomers (Scheme 3), whose stereochemistry was assigned following subsequent conversion to the *cis*- and *trans*-piperidinones, respectively (vide infra). The stereoselectivity of this radical addition is rationalized by a model directly analogous to that advanced for enolate protonation in Scheme 2. Thus, hydrogen atom transfer to the α-carbonyl radical occurs from the face opposite the more bulky alkyl chain in a conformation that minimizes $A^{1,3}$ strain, as is the case for other related diastereoselective radical reactions.[69–74]

Subsequent treatment of this mixture of diastereomers with trifluoroacetic acid removed the *tert*-butyloxycarbonyl protecting groups resulting, after removal of the acid under vacuum and treatment with base, in the cyclization of the liberated amine onto the proximal carbonyl carbon and the formation of the piperidinone skeleton bearing a thioacid substituent. Without isolation, this last species was captured by reaction with electron-deficient sulfonamides resulting overall in the piperidinonyl acetamides **24** and **25** (Scheme 4).[54,75]

3. Conclusion

Dihydro-3-(triphenylphosphoranylidene)-2,5-thiophendione is readily accessed by reaction of monothiomaleic anhydride with triphenylphosphine. It reacts with a range of aldehydes in highly *E*-selective Wittig reactions to give substituted monothioitaconic anhydride derivatives. These latter substances undergo conjugate addition reactions with *tert*-butoxycarbonylamino-derived thiols and alkyl radicals to give a series of adducts that, on treatment with trifluoroacetic anhydride followed by base, lead to thiocarboxyl-substituted heterocycles. Finally, the thiocarboxylates can be trapped in situ by reaction with 2,4-dinitrobenzenesulfonamides to give the corresponding amides.

4. Experimental section

4.1. Dihydro-3-(triphenylphosphoranylidene)-2,5-thiophendione (1)

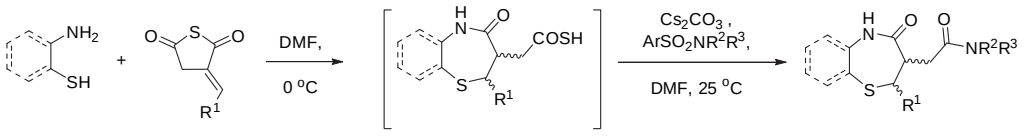
Triphenylphosphine (2.62 g, 10 mmol) was added to monothiomaleic anhydride (1.14 g, 10 mmol) in glacial acetic acid (5 mL) at room temperature and stirred for 3 h. Removal of the solvent under vacuum at room temperature and trituration of the residue with diethyl ether (3×5 mL) afforded an off-white solid in 86% yield. mp: 137–137.5 °C (decomp.); IR (film) 1700 and 1611 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.67 (m, 9H), 7.56 (dt, *J*=2.5, 7.5 Hz, 6H), 3.34 (d, *J*=1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 178.8, 133.6, 129.6, 124.8, 124.07, 50.0; ^{31}P NMR (400 MHz, $CDCl_3$) δ 12.78; ESIHRMS, *m*/*z* calcd for $C_{22}H_{17}O_2PSNa$ $(M+Na)^+$: 399.0585, found: 399.0588.

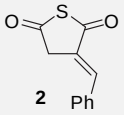
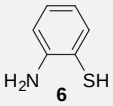
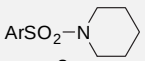
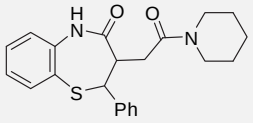
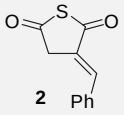
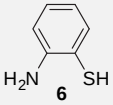
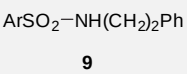
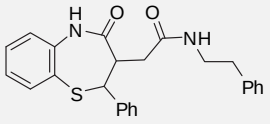
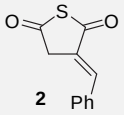
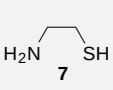
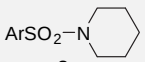
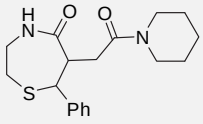
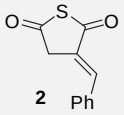
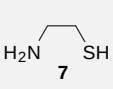
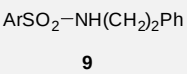
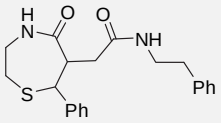
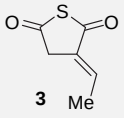
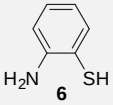
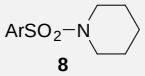
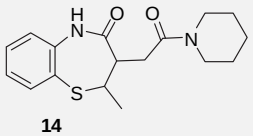
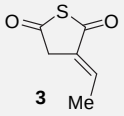
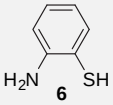
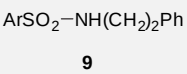
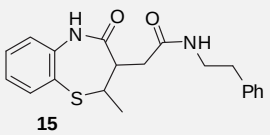
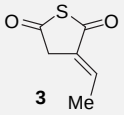
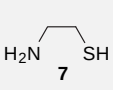
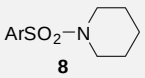
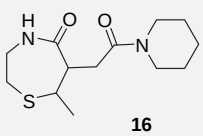
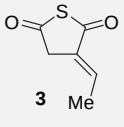
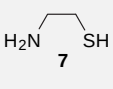
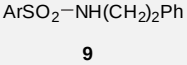
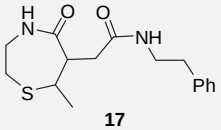
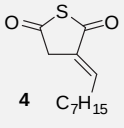
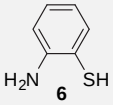
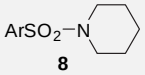
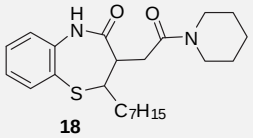
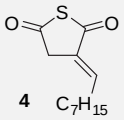
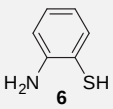
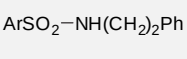
4.2. General procedure for Wittig reactions

Reagent **1** (376 mg, 1 mmol) was stirred with excess aldehyde (1 mL) at room temperature for 10 h. Excess aldehyde was removed under vacuum at room temperature and the residue was purified by chromatographic purification over silica gel, that had been prewashed with acetone followed by hexanes, to give the alkylidene monothiosuccinic anhydrides.

*4.2.1. E-2-(Benzylidene)thiosuccinic anhydride (**2**).* Rapid chromatographic purification over silica gel eluting with 10% EtOAc in hexanes afforded a pale yellow oil in 78% yield. IR (film) 1731 and 1692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (t, *J*=2.5 Hz, 1H),

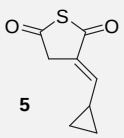
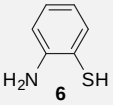
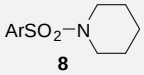
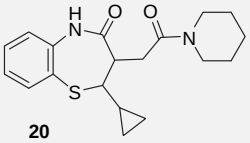
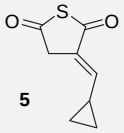
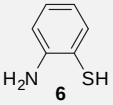
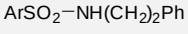
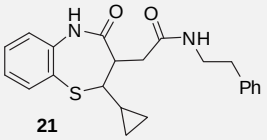
Table 2
Reaction of alkylidene monothiosuccinic anhydrides with mercaptoamines and 2,4-dinitrobenzenesulfonamides

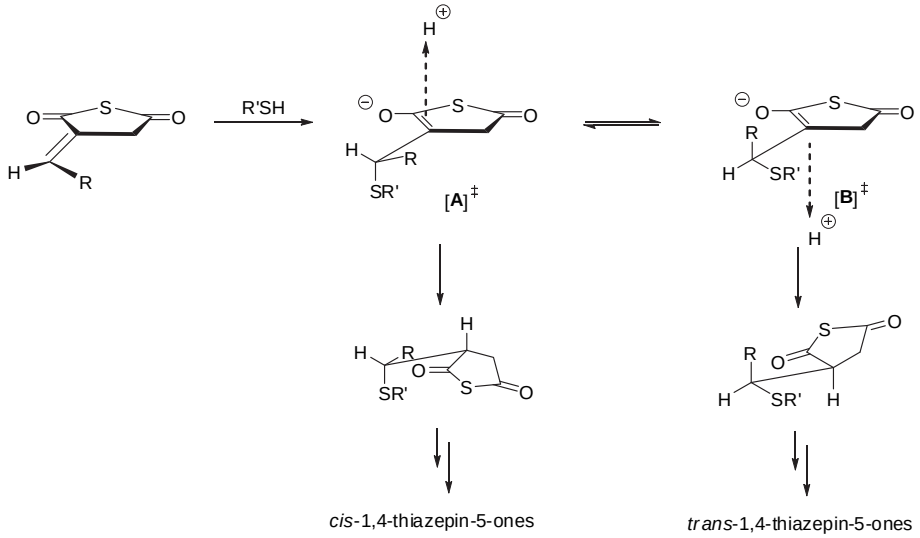


Entry	Substrate	Aminothiol	Sulfonamide ($Ar=C_6H_3(NO_2)_2$)	Product	% Yield (*cis*/*trans*) ratio
1	 **2**	 **6**	 **8**	 **10**	72 (1:5)
2	 **2**	 **6**	 **9**	 **11**	76 (1:5)
3	 **2**	 **7**	 **8**	 **12**	65 (1:4)
4	 **2**	 **7**	 **9**	 **13**	67 (1:4)
5	 **3**	 **6**	 **8**	 **14**	74 (1:1)
6	 **3**	 **6**	 **9**	 **15**	72 (1:1)
7	 **3**	 **7**	 **8**	 **16**	58 (1:1)
8	 **3**	 **7**	 **9**	 **17**	62 (1:1)
9	 **4**	 **6**	 **8**	 **18**	67 (2:5)
10	 **4**	 **6**	 **9**	**19**	61 (2:5)

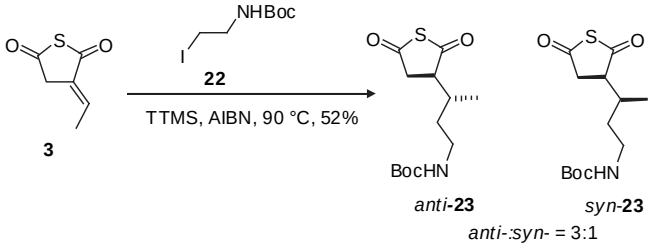
(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Aminothiol	Sulfonamide ($Ar=C_6H_3(NO_2)_2$	Product	% Yield (*cis*/*trans*) ratio
11	 **5**	 **6**	 **8**	 **20**	57 (2:3)
12	 **5**	 **6**	 **9**	 **21**	60 (2:3)



Scheme 2. Model for stereoselective protonation en route to the 1,4-thiazepin-5-ones.



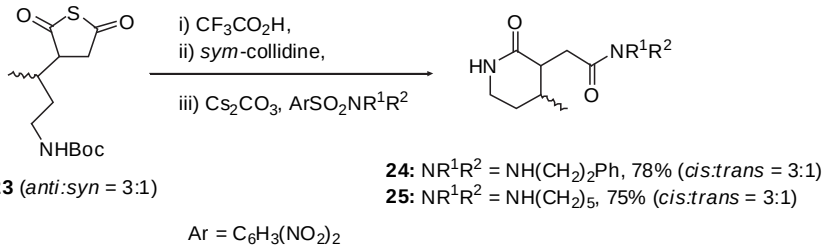
Scheme 3. Radical addition to ethylidene monothiosuccinic anhydride.

7.51–7.46 (m, 5H), 3.98 (d, J=2.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 192.7, 135.3, 133.8, 131.2, 131.1, 130.8, 130.1, 129.5, 128.4, 45.3; ESIHRMS m/z calcd for $C_{11}H_7O_2S$ $(M-1)^-$: 203.0172, found: 203.0180.

*4.2.2. E-2-(Ethylidene)thiosuccinic anhydride (**3**).* Rapid chromatographic purification over silica gel eluting with 10% EtOAc in hexanes afforded a colorless oil in 76% yield. IR (film) 1742 and 1706 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99–6.94 (m, 1H), 3.66–3.65 (m, 2H), 1.91 (dt J=2.0, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 191.3, 135.2, 134.0, 43.2, 16.5; ESIHRMS m/z calcd for $C_6H_5O_2S$ $(M-1)^-$: 141.0016, found: 141.0022.

*4.2.3. E-2-(Octylidene)thiosuccinic anhydride (**4**).* Rapid chromatographic purification over silica gel eluting with 10% EtOAc in hexanes afforded a colorless oil in 72% yield. IR (film) 1742 and 1706 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91–6.87 (m, 1H), 3.64 (dd, J=1.0, 2.5 Hz, 2H), 2.19 (q, J=7.5 Hz, 2H), 1.56–1.50 (m, 2H), 1.38–1.24 (m, 8H), 0.89 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 191.5, 140.5, 132.8, 43.3, 31.9, 31.0, 29.6, 29.2, 28.2, 22.8, 14.3; ESIHRMS m/z calcd for $C_{12}H_{17}O_2S$ $(M-1)^-$: 225.0955, found: 225.0941.

*4.2.4. E-2-(Cyclopropylmethylidene)thiosuccinic anhydride (**5**).* Rapid chromatographic purification over silica gel eluting with 10% EtOAc in hexanes afforded a colorless oil in 84% yield. IR (film) 1737 and 1699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (dt, J=11.0, 2.5 Hz, 1H), 3.77 (d, J=2.0 Hz, 2H), 1.45–1.38 (m, 1H), 1.16–1.12 (m, 2H), 0.85–



Scheme 4. Synthesis of piperidinonyl acetamides.

0.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 190.9, 145.6, 130.0, 43.6, 14.4, 10.3; ESIHRMS *m*/*z* calcd for $C_8H_7O_2S$ $(M-1)^-$: 167.0172, found: 167.0166.

4.3. General procedure for the three component coupling of alkylidene thiosuccinic anhydrides with aminothiols and 2,4-dinitrobenzenesulfonamides

The aminothiol (0.5 mmol) was added to a stirred solution of the alkylidene thiosuccinic anhydride (0.5 mmol) in DMF (5 mL) at 0 °C. The reaction mixture was stirred for overnight at 0 °C before Cs_2CO_3 (0.6 mmol) was added, followed immediately by the sulfonamide (0.5 mmol). Stirring was continued while the reaction mixture was allowed to warm to room temperature and the subsequently for a further 1 h. The solvent was then removed under vacuum and the residue was dissolved in ethyl acetate, washed with water followed by brine, and dried over Na_2SO_4. Purification was then realized by silica gel column chromatography.

*4.3.1. cis- and trans-N-[(Benzo[b]-5-oxo-7-phenyl-1,4-thiazepin-6yl)acetyl]piperidine (**10**).* Chromatographic purification by eluting with 70% ethyl acetate in hexanes afforded the trans and cis isomers with yields of 60% and 12%, respectively.

trans-Isomer: pale yellow solid, mp 226–227 °C; IR (film) 1678 and 1631 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J*=7.5 Hz, 1H), 7.44 (t, *J*=7.7 Hz, 1H), 7.35 (d, *J*=7.5 Hz, 1H), 7.30–7.24 (m, 3H), 7.20 (t, *J*=7.2 Hz, 2H), 7.11 (d, *J*=7.5 Hz, 2H), 4.32 (d, *J*=12.5 Hz, 1H), 3.61 (dt, *J*=2.0, 11.5 Hz, 1H), 3.46–3.39 (m, 1H), 3.36–3.24 (m, 2H), 3.18–3.12 (m, 1H), 3.08 (dd, *J*=11.0, 16.0 Hz, 1H), 1.80 (d, *J*=16.0 Hz, 1H), 1.56–1.32 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 169.0, 143.4, 141.7, 136.0, 130.8, 129.2, 128.1, 126.7, 126.6, 126.3, 124.0, 56.9, 46.5, 44.6, 43.0, 33.9, 26.3, 25.6, 24.6; ESIHRMS *m*/*z* calcd for $C_{22}H_{24}N_2O_2SNa$ $(M+Na)^+$: 403.1456, found: 403.1473.

cis-Isomer: yellow solid, mp163–164 °C; IR (film) 1676 and 1637 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J*=1.5, 8.0 Hz, 1H), 7.54 (br s, 1H), 7.51 (d, *J*=7.0 Hz, 2H), 7.42–7.34 (m, 4H), 7.21 (t, *J*=7.0 Hz, 2H), 5.02 (d, *J*=7.0 Hz, 1H), 3.66–3.61 (m, 1H), 3.59–3.54 (m, 1H), 3.34–3.29 (m, 1H), 3.17–3.07 (m, 2H), 3.53(dd, *J*=8.0, 16.5 Hz, 1H), 2.07 (dd, *J*=5.5, 16.5 Hz, 1H), 1.55–1.37 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 168.6, 141.9, 137.2, 135.3, 130.6, 129.7, 128.8, 128.6, 126.7, 123.4, 57.8, 46.5, 43.0, 42.1, 32.9, 26.3, 25.7, 24.7; ESIHRMS *m*/*z* calcd for $C_{22}H_{24}N_2O_2SNa$ $(M+Na)^+$: 403.1456, found: 403.1469.

*4.3.2. cis- and trans-N-(2-Phenylethyl) (benzo[b]-5-oxo-7-phenyl-1,4-thiazepin-6yl)acetamide (**11**).* Chromatographic purification eluting with 70% ethyl acetate in hexanes afforded the trans and cis isomers with yields of 63% and 13%, respectively.

trans-Isomer: pale yellow solid, mp 214–215 °C; IR (film) 1665 and 1642 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J*=8 Hz, 1H), 7.50–7.45 (m, 2H), 7.34–7.26 (m, 5H), 7.24–7.20 (m, 2H), 7.14 (d, *J*=7.5 Hz, 3H), 7.09 (d, *J*=6.5 Hz, 2H), 5.56 (br s, 1H), 4.27 (d, *J*=12 Hz, 1H), 3.55 (dt, *J*=2.5, 11.5 Hz, 1H), 3.39 (q, *J*=6.5 Hz, 2H), 2.73–2.65 (m, 3H), 1.82 (dd, *J*=2.5, 15 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 170.7, 142.9, 141.1, 139.0, 136.2, 130.8, 129.3, 129.0, 128.8, 128.2, 127.1, 126.7, 126.4, 123.9, 57.1, 44.9, 40.8, 36.6, 35.8; ESIHRMS *m*/*z* calcd for $C_{25}H_{24}N_2O_2SNa$ $(M+Na)^+$: 439.1456, found: 439.1457.

cis-Isomer: pale yellow solid, mp 151–151.5 °C; IR (film) 1671 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J*=6.5 Hz, 1H), 7.60 (br s, 1H), 7.47–7.38 (m, 3H), 7.35–7.28 (m, 4H), 7.24–7.12 (m, 6H), 5.45 (br s, 1H), 4.94 (d, *J*=7.0 Hz, 1H), 3.57–3.52 (m, 1H), 3.47–3.34 (m, 2H), 2.72 (t, *J*=7.0 Hz, 2H), 2.28 (dd, *J*=9.0, 15.0 Hz, 1H), 1.89 (dd, *J*=5.0, 15.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 170.7, 141.5, 138.9, 136.8, 135.4, 130.6, 129.7, 128.9, 128.8, 128.4, 127.0, 126.7, 123.4, 58.2, 42.5, 40.1, 36.2, 35.7; ESIHRMS *m*/*z* calcd for $C_{25}H_{24}N_2O_2SNa$ $(M+Na)^+$: 439.1456, found: 439.1462.

*4.3.3. cis- and trans-N-[(5-Oxo-7-phenyl-1,4-thiazepin-6yl)acetyl]piperidine (**12**).* Chromatographic purification eluting with 4% methanol in dichloromethane afforded the trans and cis isomers with yields of 52% and 13%, respectively.

trans-Isomer: light yellow gum, IR (film) 1675 and 1614 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 7.22–7.19 (m, 3H), 5.85 (br s, 1H), 4.15 (d, *J*=9.5 Hz, 1H), 3.66–3.54 (m, 2H), 3.52–3.43 (m, 2H), 3.33–3.28 (m, 1H), 3.14–3.05 (m, 3H), 2.96–2.85 (m, 3H), 1.50–1.18 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 171.6, 139.4, 129.7, 128.5, 126.7, 47.0, 43.8, 43.4, 43.0, 42.0, 37.3, 28.5, 25.5, 24.6; ESIHRMS *m*/*z* calcd for $C_{18}H_{24}N_2O_2SNa$ $(M+Na)^+$: 355.1456, found: 355.1445.

cis-Isomer: light yellow gum, IR (film) 1638 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 5.95 (t, *J*=6.5 Hz, 1H), 4.10–4.00 (m, 2H), 3.89 (d, *J*=10.0 Hz, 1H), 3.68–3.61 (m, 1H), 3.52–3.46 (m, 1H), 3.44–3.36 (m, 1H), 3.28–3.22 (m, 1H), 3.16–3.10 (m, 1H), 2.97–2.89 (m, 1H), 2.87–2.81 (m, 2H), 1.88 (dd, *J*=3.0, 16.0 Hz, 1H), 1.58–1.30 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 169.5, 140.5, 131.6, 129.3, 129.1, 128.1, 128.0, 47.3, 46.5, 46.0, 43.2, 43.0, 34.0, 32.1, 26.3, 25.6, 24.7; ESIHRMS *m*/*z* calcd for $C_{18}H_{24}N_2O_2SNa$ $(M+Na)^+$: 355.1456, found: 355.1454.

*4.3.4. cis- and trans-N-(2-Phenylethyl) (5-oxo-7-phenyl-1,4-thiazepin-6yl)acetamide (**13**).* Chromatographic purification eluting with 4% methanol in dichloromethane afforded a pale yellow gum in 67% yield as 1:4 *cis*/*trans*-mixture.

trans-Isomer: IR (film) 1666 and 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 7H), 7.24–7.19 (m, 2H), 7.16 (d, *J*=7.0 Hz, 2H), 6.01 (br s, 1H), 5.52 (br s, 1H), 4.02–3.84 (m, 3H), 3.66–3.60 (m, 1H), 3.49–3.35 (m, 2H), 2.96–2.87 (m, 1H), 2.82–2.71 (m, 2H), 2.43 (dd, *J*=11.0, 14.7 Hz, 1H), 1.91 (dd, *J*=3.2, 14.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 171.5, 139.9, 139.0, 129.1, 129.0, 128.8, 128.3, 128.1, 126.6, 46.3, 43.6, 40.9, 37.5, 35.8, 32.5; ESIHRMS *m*/*z* calcd for $C_{21}H_{24}N_2O_2SNa$ $(M+Na)^+$: 391.1456, found: 391.1449.

cis-Isomer: the minor *cis*-isomer was identified in the mixture by characteristic signals at δ 6.09 (br s, 1H), 5.63 (br s, 1H), 3.06–3.01 (m, 1H), 2.53 (dd, *J*=8.2, 14.7 Hz, 1H), 2.09 (dd, *J*=4.7, 14.7 Hz, 1H) in the ^{1}H NMR spectrum, and by δ 175.2, 171.2, 139.3, 128.7, 128.2, 126.7, 48.0, 45.9, 40.7, 38.1, 29.8 in the ^{13}C NMR spectrum.

*4.3.5. cis- and trans-N-[(Benzo[b]-5-oxo-7-methyl-1,4-thiazepin-6yl)acetyl]piperidine (**14**).* Chromatographic purification eluting

with 70% ethyl acetate in hexanes afforded a pale yellow solid in 74% yield as 1:1 *cis*/*trans*-mixture.

trans-Isomer: IR (film) 1674 and 1633 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, J=1.5, 7.5 Hz, 1H), 7.42 (br s, 1H), 7.40–7.32 (m, 1H), 7.24 (d, J=7.0 Hz, 1H), 7.19–7.13 (m, 1H), 3.57–3.51 (m, 1H), 3.47–3.38 (m, 2H), 3.33–3.27 (m, 1H), 3.16 (dd, J=10.5, 16 Hz, 1H), 2.92 (dt, J=2.5, 11 Hz, 1H), 2.24 (dd, J=2.7, 16.2 Hz, 1H), 1.65–1.42 (m, 6H), 1.39 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 169.1, 141.5, 136.6, 135.0, 130.7, 128.3, 126.5, 125.8, 123.7, 48.3, 47.7, 46.7, 45.9, 43.2, 33.6, 26.5, 23.1, 16.9; ESIHRMS m/z calcd for $C_{17}H_{22}N_2O_2SNa$ $(M+Na)^+$: 341.1300, found: 341.1291.

cis-Isomer: the *cis*-isomer was identified in the mixture by characteristic signals at δ 7.57 (dd, J=12.0, 7.7 Hz, 1H), 3.95–3.87 (m, 1H), 2.17 (dd, J=3.7, 16.2 Hz, 1H), 1.37 (d, J=6.5 Hz, 3H) in the ^1H NMR spectrum, and by δ 173.3, 168.7, 141.8, 123.4, 126.4, 130.2, 47.7, 43.1, 41.5, 32.5, 25.7, 24.7 in the ^{13}C NMR spectrum.

*4.3.6. cis- and trans-N-(2-Phenylethyl) (benzo[b]-5-oxo-7- methyl -1,4-thiazepin-6yl)acetamide (**15**).* Chromatographic purification eluting with 70% ethyl acetate in hexanes afforded a pale yellow oil in 72% yield as 1:1 *cis*/*trans*-mixture.

trans-Isomer: IR (film) 1670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J=7.5 Hz, 1H), 7.57–7.30 (m, 4H), 7.25–7.14 (m, 5H), 6.15 (br s, 1H), 3.50–3.40 (m, 2H), 3.26–3.20 (m, 1H), 2.82–2.76 (m, 3H), 2.70 (dd, J=10.5, 14.5 Hz, 1H), 2.30 (dd, J=2.2, 14.2 Hz, 1H), 1.39 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 170.8, 141.3, 139.0, 136.7, 130.7, 129.0, 128.8, 126.8, 125.8, 123.6, 48.0, 46.6,, 41.0, 35.9, 35.6, 23.0, 16.5; ESIHRMS m/z calcd for $C_{20}H_{22}N_2O_2SNa$ $(M+Na)^+$: 377.1300, found: 377.1284.

cis-Isomer: the *cis*-isomer was identified in the mixture by characteristic signals at δ 7.57 (d, J=7.5 Hz, 1H), 7.08 (d, J=7.5 Hz, 1H), 5.72 (br s, 1H), 3.87 (q, J=6.5 Hz, 1H), 3.36–3.32 (m, 2H), 2.06 (dd, J=3.5, 14.7 Hz, 1H), 1.31 (d, J=6.5 Hz, 3H) in the ^1H NMR spectrum, and by δ 175.1, 170.9, 141.1, 139.2, 135.1, 130.2, 128.1, 126.7, 123.4, 48.8, 42.3, 40.8, 36.5, 35.87 in the ^{13}C NMR spectrum.

*4.3.7. cis- and trans-N-[(5-Oxo-7-methyl-1,4-thiazepin-6yl)acetyl]piperidine (**16**).* Chromatographic purification eluting with 4% methanol in dichloromethane afforded a pale yellow oil in 58% yield as 1:1 *cis*/*trans*-mixture.

trans-Isomer: IR (film) 1663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (br s, 1H), 3.93–3.97(m, 1H), 3.60–3.49 (m, 5H), 3.40 (dt, J=3.5, 9.7 Hz, 1H), 3.11–3.05 (m, 1H), 2.98 (dd, J=11.7, 14.2 Hz, 1H), 2.54 (dd, J=11.5, 14.5 Hz, 1H), 2.37 (dd, J=3.2, 16.2 Hz, 1H), 1.70–1.51 (m, 6H), 1.38 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 169.2, 48.5, 46.7, 45.7, 43.1, 36.0, 33.2, 26.6, 25.8, 24.8, 20.3, 16.7; ESIHRMS m/z calcd for $C_{13}H_{22}N_2O_2SNa$ $(M+Na)^+$: 293.1300, found: 293.1284.

cis-Isomer: the *cis*-isomer was identified in the mixture by characteristic signals at δ 5.87 (br s, 1H), 4.03 (dd, J=5.5, 8.0 Hz, 1H), 3.80–3.73 (m, 1H), 3.48–3.41 (m, 5H), 2.88 (dt, J=4.5, 14.5 Hz, 1H), 2.83–2.74 (m, 3H), 2.24 (dd, J=5.5, 16.0 Hz, 1H), 1.37 (d, J=7.0 Hz, 3H) in the ^1H NMR spectrum, and by δ 176.9, 169.4, 48.3, 46.8, 43.2, 42.2, 35.9, 34.7, 27.3, 26.5, 25.7 in the ^{13}C NMR spectrum.

*4.3.8. cis- and trans-N-(2-Phenylethyl) (5-oxo-7-methyl-1,4-thiazepin-6yl)acetamide (**17**).* Chromatographic purification eluting with 4% methanol in dichloromethane afforded a pale yellow oil in 62% yield as 1:1 *cis*/*trans*-mixture.

trans-Isomer: IR (film) 1649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J=7.5 Hz, 2H), 7.24–7.19 (m, 3H), 6.09 (br s, 1H), 5.96 (br s, 1H), 3.83–3.77 (m, 1H), 3.66–3.59 (m, 1H), 3.57–3.44 (m, 3H), 2.87 (dt, J=4.2, 19.7 Hz, 1H), 2.82–2.77 (m, 4H), 2.52 (dd, J=5.5, 15.0 Hz, 1H), 2.16 (dd, J=4.7, 14.2 Hz, 1H), 1.33 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 171.2, 139.2, 129.0, 126.7, 49.2, 45.8, 42.2, 40.9, 38.6, 37.0, 36.2, 26.9, 20.3, 16.5; ESIHRMS m/z calcd for $C_{16}H_{22}N_2O_2SNa$ $(M+Na)^+$: 329.1300, found: 329.1302.

cis-Isomer: the *cis*-isomer was identified in the mixture by characteristic signals at δ 6.07 (br s, 1H), 5.94–5.90 (m, 1H), 3.89 (dd, J=4.5, 9.5 Hz, 1H), 3.27–3.21 (m, 1H), 2.94 (dd, J=10.7, 15.0 Hz, 1H), 2.75–2.66 (m, 2H), 2.38 (dd, J=3.7, 14.2 Hz, 1H),1.38 (d, J=7.0 Hz, 3H) in the ^1H NMR spectrum, and by δ 176.5, 171.3, 139.1, 128.8, 126.6, 49.1, 40.8, 36.3, 35.9, 28.9 in the ^{13}C NMR spectrum.

*4.3.9. cis- and trans-N-[(Benzo[b]-5-oxo-7-octanyl-1,4-thiazepin-6yl)acetyl]piperidine (**18**).* Chromatographic purification eluting with 70% ethyl acetate in hexanes afforded a pale yellow oil in 67% yield as 2:5 *cis*/*trans*-mixture.

trans-Isomer: IR (film) 1677 and 1641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (t, J=8.0 Hz, 1H), 7.51 (br s, 1H), 7.34–7.31 (m, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.17–7.12 (m, 1H), 3.53–3.36 (m, 4H), 3.19–3.09 (m, 1H), 3.00 (dt, J=2.0, 11.0 Hz, 1H), 2.26 (d, J=15.5 Hz, 1H), 1.84–1.70 (m, 1H), 1.50–1.56 (m, 4H), 1.56–1.40 (m, 5H), 1.40–1.14 (m, 9H), 0.92–0.83 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 169.2, 141.8, 136.6, 130.6, 126.4, 126.3, 123.6, 54.2, 46.7, 44.6, 43.2, 43.1, 34.9, 33.5, 32.0, 29.8, 29.4,, 26.5, 25.7, 24.8, 22.9, 14.3; ESIHRMS m/z calcd for $C_{23}H_{34}N_2O_2SNa$ $(M+Na)^+$: 425.2239, found: 425.2249.

cis-Isomer: the *cis*-isomer was identified in the mixture by characteristic signals at δ 7.65 (br s, 1H), 7.32 (t, J=7.5 Hz, 3H), 7.05 (d, J=7.5 Hz, 1H), 3.78–3.74 (m, 1H), 2.16 (dd, J=3.2, 16.2 Hz, 1H) in the ^1H NMR spectrum, and by δ 173.6, 168.8, 135.1, 130.0, 128.1, 123.4, 53.6, 41.4, 32.7, 27.7, 26.4, 24.7 in the ^{13}C NMR spectrum.

*4.3.10. cis- and trans-N-(2-Phenylethyl) (benzo[b]-5-oxo-7-octanyl -1,4-thiazepin-6yl)acetamide (**19**).* Chromatographic purification eluting with 70% ethyl acetate in hexanes afforded a pale yellow oil in 61% yield as 2:5 *cis*/*trans*-mixture.

trans-Isomer: IR (film) 1672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61–7.54 (m, 2H), 7.38 (dt, J=1.5, 7.5 Hz, 1H), 7.35–7.30 (m, 3H), 7.25–7.14 (m, 4H), 6.18 (br s, 1H), 3.54–3.41 (m, 2H), 3.06 (t, J=10.0 Hz, 1H), 2.88–2.70 (m, 4H), 2.32 (dd, J=2.5, 14.0 Hz, 1H), 1.67–1.52 (m, 2H), 1.45–1.20 (m, 10H), 0.92–0.88 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 171.1, 141.4, 139.2, 136.7, 135.3, 130.6, 129.0, 128.5, 126.8, 126.7, 123.6, 54.6, 45.3, 40.9, 36.6, 35.8, 34.7, 32.0, 29.7, 29.4, 26.4, 22.9, 14.3; ESIHRMS m/z calcd for $C_{26}H_{34}N_2O_2SNa$ $(M+Na)^+$: 461.2239, found: 461.2261.

cis-Isomer: the *cis*-isomer was identified in the mixture by characteristic signals at δ 7.66 (br s, 1H), 7.07 (d, J=8.0 Hz, 1H), 5.76 (br s, 1H), 3.77–3.72 (m, 1H), 3.40–3.35 (m, 1H), 2.06 (dd, J=3.7, 14.2 Hz, 1H), 1.78–1.72 (m, 1H) in the ^1H NMR spectrum, and by δ 173.2, 170.8, 141.2, 139.0, 130.1, 126.4, 123.3, 53.8, 42.2, 31.7, 27.5 in the ^{13}C NMR spectrum.

*4.3.11. cis- and trans-N-[(Benzo[b]-5-oxo-7-cyclopropyl-1,4-thiazepin-6yl)acetyl]piperidine (**20**).* Chromatographic purification eluting with 70% ethyl acetate in hexanes afforded a pale yellow oil in 57% yield as 2:3 *cis*/*trans*-mixture.

trans-Isomer: IR (film) 1677 and 1638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, J=1.0, 7.5 Hz, 1H), 7.38–7.31 (m, 2H), 7.24–7.12 (m, 2H), 3.58–3.35 (m, 5H), 3.26 (dd, J=3.0, 11.5 Hz, 1H), 3.20–3.15 (m, 1H), 3.09 (dd, J=11.0, 16.0 Hz, 1H), 2.46 (dd, J=5.0, 16.5 Hz, 1H), 1.52–1.40 (m, 6H), 0.76–0.60 (m, 2H), 0.35–0.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 169.0, 141.6, 135.1, 130.1, 126.6, 123.5, 59.0, 45.3, 42.4, 32.8, 25.7, 24.7, 18.4, 12.5, 7.1, 3.9, ESIHRMS m/z calcd for $C_{19}H_{24}N_2O_2SNa$ $(M+Na)^+$: 367.1456, found: 367.1450.

cis-Isomer: the minor *cis*-isomer was identified in the mixture by characteristic signals at δ 7.63 (dd, J=1.0, 4.5 Hz, 1H), 2.73–2.67 (m, 1H), 0.53–0.48 (m, 2H) in the ^1H NMR spectrum, and by δ 174.8,

169.4, 141.3, 136.1, 130.4, 128.7, 126.4, 123.4, 59.4, 46.7, 43.1, 33.5, 26.5, 9.0, 3.1 in the ^{13}C NMR spectrum.

*4.3.12. cis- and trans-N-(2-Phenylethyl) (benzo[b]-5-oxo-7-cyclopropyl-1,4-thiazepin-6yl)acetamide (**21**).* Chromatographic purification eluting with 70% ethyl acetate in hexanes afforded a pale yellow oil in 60% yield as 2:3 *cis*/*trans*-mixture.

trans-Isomer, IR (film) 1671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J=1.0, 7.5 Hz, 1H), 7.40–7.30 (m, 4H), 7.25–7.15 (m, 5H), 5.93 (br s, 1H), 3.53–3.45 (m, 2H), 3.22–3.17 (m, 1H), 2.79 (q, J=7.0 Hz, 2H), 2.70 (d, J=7.0 Hz, 2H), 1.04–0.97 (m, 1H), 0.77–0.59 (m, 3H), 0.32–0.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 171.3, 140.8, 139.2, 136.2, 130.4, 129.0, 128.9, 128.8 126.4, 123.4, 59.5, 45.9, 40.9, 36.7, 35.9, 31.5, 18.2, 9.0, 3.8; ESIHRMS m/z calcd for $C_{22}H_{24}N_2O_2SNa$ $(M+Na)^+$: 403.1456, found: 403.1472.

cis-Isomer: the minor *cis*-isomer was identified in the mixture by characteristic signals at δ 7.56 (dd, J=1.2, 7.7 Hz, 1H), 7.09 (d, J=7.5 Hz, 1H), 5.72 (br s, 1H), 3.42–3.38 (m, 1H), 3.11 (dd, J=5.5, 10.5 Hz, 1H), 3.00 (dd, J=9.7, 14.7 Hz, 1H), 2.64 (dd, J=9.5, 11.5 Hz, 1H), 2.26 (dd, J=4.5, 14.5 Hz, 1H), 1.19–1.14 (m, 1H), 0.92–0.86 (m, 1H), 0.51–0.46(m, 1H) in the ^1H NMR spectrum, and by δ 173.5, 171.1, 141.2, 135.1, 130.2, 128.5, 126.8, 126.7, 123.5, 59.4, 43.1, 35.9, 25.9, 12.4, 7.2, 3.0 in the ^{13}C NMR spectrum.

*4.3.13. 2-[3-(tert-Butyloxycarbonylamino)-2-methylpropyl]succinic thioanhydride (**23**).* Tris(trimethylsilyl)silane (373 mg, 1.5 mmol) and AIBN (33 mg, 0.2 mmol) in dry degassed toluene (5 mL) were added drop-wise to a stirred mixture of **22** (407 mg, 1.5 mmol) and **3** (142 mg, 1 mmol) in dry degassed toluene (10 mL) at 90 °C over 5 h by syringe pump under a N_2 atmosphere. When the addition was complete, the reaction mixture was allowed to stir for an additional 1 h at 90 °C before it was cooled to room temperature and the solvent was removed under vacuum. Rapid chromatographic purification over silica gel, pre-washed with acetone followed by hexanes, eluting with 30% ethyl acetate in hexanes afforded a colorless oil in 52% yield as a 3:1 inseparable *anti*/*syn* diastereomeric mixture.

anti-Isomer: IR (film) 1708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.58 (br s, 1H), 3.55–3.02 (m, 4H), 2.88 (dd, J=4.0, 6.5 Hz, 1H), 2.26–2.18 (m, 1H), 1.66–1.58 (m, 1H), 1.54–1.41 (m, 10H), 1.04 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 199.9, 156.2, 79.6, 57.4, 44.4, 38.6, 35.7, 33.3, 28.6, 17.2; ESIHRMS m/z calcd for $C_{13}H_{21}NO_4SNa$ $(M+Na)^+$: 310.1089, found: 310.1082.

syn-Isomer: the minor *syn*-isomer was identified in the mixture by characteristic signals at δ 2.84 (dd, J=4.0, 6.5 Hz, 1H), 2.44–2.36 (m, 1H), 0.96 (d, J=7.0 Hz, 3H) in the ^1H NMR spectrum, and by δ 199.8, 56.9, 42.3, 38.3, 32.6, 31.5, 14.7 in the ^{13}C NMR spectrum.

4.4. General procedure for piperidinone synthesis from the radical adduct 23

To a stirred solution of **23** (145 mg, 0.5 mmol) in dichloromethane (20 mL) at 0 °C, trifluoroacetic acid (5 mL) was added drop-wise. Stirring was maintained for 1 h before the acid was removed by azeotropic distillation with toluene (5 mL×3), after which the residue was dried under vacuum. The residue was dissolved in DMF (20 mL) and cooled down to 0 °C before 2,4,6-collidine (0.090 mg, 0.75 mmol) was added drop-wise and the reaction mixture was stirred for 1 h at 0 °C. The resulting reaction mixture was maintained at 0 °C, and Cs_2CO_3 (0.195 mg, 0.6 mmol) followed by the sulfonamide (0.6 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1.5 h before the solvent was removed under vacuum and the residue was dissolved in EtOAc (30 mL). The organic layer was washed successively with water and brine, dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography.

*4.4.1. N-(2-Phenylethyl) (4-methyl-2-oxopiperidin-3-yl)acetamide (**24**).* Chromatographic purification eluting with 4% methanol in dichloromethane afforded a pale yellow solid in 78% yield as a 3:1 *cis*/*trans*-mixture.

cis-Isomer: IR (film) 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, J=7.5 Hz, 2H), 7.24–7.19 (m, 3H), 6.86 (br s, 1H), 5.78 (br s, 1H), 3.54–3.45 (m, 2H), 3.38 (dt, J=5.5, 11.5 Hz, 1H), 3.32–3.23 (m, 1H), 2.84–2.79 (m, 2H), 2.77–2.70 (m, 1H), 2.28–2.21 (m, 1H), 2.09 (dd, J=4.5, 14.5 Hz, 1H), 2.01–1.94 (m, 1H), 1.88–1.78 (m, 2H), 0.93 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 172.6, 139.4, 129.0, 126.5, 43.4, 40.9, 39.1, 36.4, 35.9, 30.6, 28.9, 13.9; ESIHRMS m/z calcd for $C_{16}H_{22}N_2O_2Na$ $(M+Na)^+$: 297.1579, found: 297.1591.

trans-Isomer: the minor *trans*-isomer was identified in the mixture by characteristic signals at δ 6.50 (br s, 1H), 5.85 (br s, 1H),2.50 (dd, J=6.0, 14.5 Hz, 1H), 2.18–2.14 (m, 1H), 1.72–1.66 (m, 1H) 1.1 (d, J=6.5 Hz, 3H) in the ^1H NMR spectrum, and by δ 174.4, 171.9, 139.3, 129.0, 128.7, 46.6, 41.3, 40.7, 36.0, 35.8, 31.9, 30.7, 20.4 in the ^{13}C NMR spectrum.

*4.4.2. N-[(4-Methyl-2-oxopiperidin-3-yl)acetyl]piperidine (**25**).* Chromatographic purification eluting with 4% methanol in dichloromethane afforded the *cis*- and *trans*-isomers with yields of 56% and 19%, respectively.

cis-Isomer: light yellow gum, IR (film) 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.63 (br s, 1H), 3.64–3.59 (m, 1H), 3.56–3.39 (m, 4H), 3.34–3.29 (m, 1H), 3.14–3.09 (m, 2H), 2.43–2.37 (m, 1H), 2.27 (dd, J=9.7, 17.2 Hz, 1H), 2.09–2.03 (m, 1H), 1.75–1.52 (m, 7H), 0.96 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 170.0, 46.8, 43.1, 42.9, 38.9, 30.6, 29.3, 28.5, 26.7, 25.8, 24.9, 14.0; ESIHRMS m/z calcd for $C_{13}H_{22}N_2O_2Na$ $(M+Na)^+$: 261.1579, found: 261.1561.

trans-Isomer: light yellow gum, IR (film) 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (br s, 1H), 3.59–3.40 (m, 5H), 3.32–3.26 (m, 1H), 2.94 (dd, J=5.5, 16.5 Hz, 1H), 2.70 (dd, J=3.2, 16.2 Hz, 1H), 2.26–2.20 (m, 1H), 2.17–2.12 (m, 1H), 1.85 (dd, J=3.2, 13.2 Hz, 1H), 1.68–1.50 (m, 7H), 1.02 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 169.6, 46.7, 45.6, 43.0, 41.2, 37.9, 32.1, 31.5, 31.1, 29.9, 26.6, 25.8, 24.8, 20.6; ESIHRMS m/z calcd for $C_{13}H_{22}N_2O_2Na$ $(M+Na)^+$: 261.1579, found: 261.1564.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.002.

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