# Regioselective Preparation of 1-(Bromomethyl)-5*H*-thiazolo[3,2-*a*]quinazolin-5-ones and Analogous 5*H*-Thieno[3,2-*e*]thiazolo[3,2-*a*]pyrimidin-5-ones from Fused 2-(Alkenylthio)pyrimidin-4-ones

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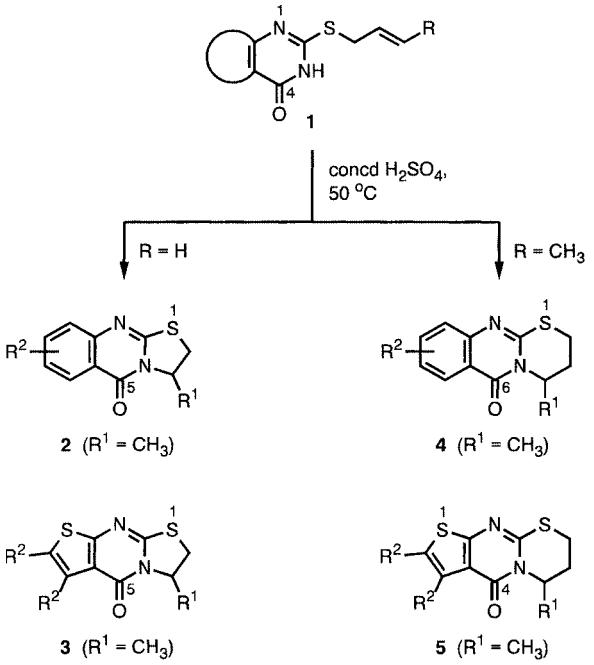
**Abstract:** A convenient procedure for the regioselective preparation of polycyclic angular thiazolo[3,2-*a*]pyrimidin-5-ones is reported. 2-(Alkenylthio)quinazolin-4(3*H*)-ones and analogues thieno[2,3-*d*]pyrimidines were treated with bromine in acetic acid to obtain 1-(bromomethyl)-5*H*-thiazolo[3,2-*a*]quinazolin-5-ones **8a**,**d**, and 1-(bromomethyl)-5*H*-thieno[3,2-*e*]thiazolo[3,2-*a*]pyrimidin-5-ones **8b**,**c**,**e**,**f**, respectively. A route starting from 2-(alkenylamino)benzamides, which were converted to corresponding 2-thioxoquinazolin-4-ones and subsequently treated with bromine in acetic acid furnished angular 2-(bromomethyl)thiazolo[3,2-*a*]quinazolin-5-ones **11**, or 3-(bromomethyl)[1,3]thiazino[3,2-*a*]quinazolin-6-one **14**, respectively.

**Key words:** polycyclic pyrimidinones, thiazolo[3,2-*a*]quinazolin-5-ones, thieno[3,2-*e*]thiazolo[3,2-*a*]pyrimidin-5-ones; bromocyclization, 2-(alkenylthio)pyrimidin-4-ones, heterocycles

Bicyclic and tricyclic thiazolo(1,3-thiazino)-pyrimidinones[1] have been found to exhibit various biological activities[2] and are useful intermediates for the preparation of immunostimulating mercaptoalkyl pyrimidinediones,[6,7] or heterocyclic substituted alkyl disulfides.[8] Recently, the anti-HIV-1 activity of 2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-ones has been described.[5] In a previous paper,[3] we have reported on the regioselective cyclization of 2-allylthioquinazolinones (and thieno[2,3-*d*]pyrimidinones) **1** to 2,3-dihydro-3-methyl-5*H*-thiazolo[2,3-*b*]quinazolinones **2** and analogous thienopyrimidinones **3** (Scheme 1). These linear thiazolo compounds were obtained exclusively by an acid-catalyzed reaction on treating allyl derivatives **1** with concentrated sulfuric acid. Linear 4-methyl-[1,3]thiazino[2,3-*b*]quinazolinones **4** and analogous thienopyrimidinones **5** were prepared from the corresponding 2-*trans*-crotyl derivatives **1**. Herein, we wish to report on the cyclization of 2-alkenylthio substituted quinazolin-4-ones and thieno[2,3-*d*]pyrimidin-4-ones upon treatment with bromine.

The required alkenylthio derivatives **7a**–**f** were conveniently obtained on reacting the corresponding 2-thioxo derivatives **6** with alkenyl halides (Scheme 2). Their tautomeric form such as 3*H*-pyrimidin-4-ones was concluded from UV and NMR data.[9] In addition to the starting compounds **7**, 1-alkenyl-2-thioxoquinazolin-4-ones **10a**–**c** and **13** were considered to be used as substrates for cyclization reactions with bromine. Attempts to obtain these compounds by reacting 2-(alkenylamino)benzamides

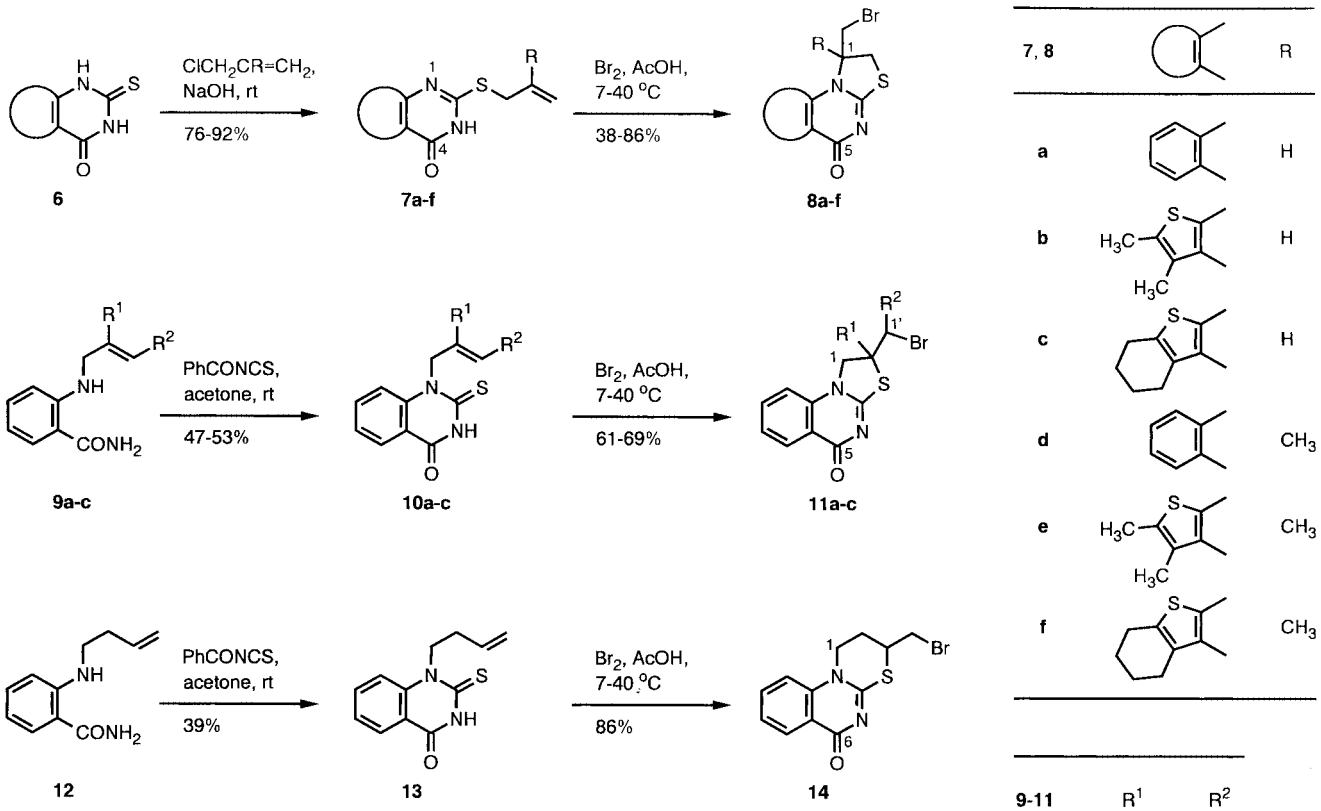



**Scheme 1**

**9a**–**c**, **12** with thiophosgene, or potassium ethyl xanthogenate were not successful. However, the introduction of the C=S unit was achieved on treatment with benzoyl isothiocyanate to furnish **10a**–**c, 13** in moderate yields (Table 1).

The alkenyl derivatives **7**, **10**, and **13** were reacted with bromine in acetic acid. This procedure turned out to be a convenient access to polycyclic bromomethyl substituted thiazolo- or 1,3-thiazinopyrimidinones. In most of the transformations, the products were either formed without remarkable impurities, or the main products could be isolated in sufficient yields without column chromatography. The structural assignment of the products **8**, **11**, **14** was based on elemental analyses, MS, UV, and NMR data. As expected, upon treatment with bromine, bromocyclization occured to result in a loss of the double bond and the condensation of an additional bromo-, or bromoalkyl substituted ring.

For example, in the transformation of **7a** or **7d**, four possible isomeric products, with a linear or angular, as well as five-membered or six-membered ring had to be considered. However, treatment of **7a** or **7d** with bromine result-




| 7, 8 | | R |
|---|---|---|
| a | | H |
| b | | H |
| c | | H |
| d | | $CH_3$ |
| e | | $CH_3$ |
| f | | $CH_3$ |

| 9-11 | $R^1$ | $R^2$ |
|---|---|---|
| a | H | H |
| b | $CH_3$ | H |
| c | H | $CH_3$ |

**Scheme 2**

ed in the regioselective formation of the angular thiazolo compounds **8a**, **8d**, respectively, whose structural elucidation was achieved as follows. The UV spectra of the products showed three maxima at λ = 231−232, 256, and λ = 307 nm (Table 1). Maxima were consistent (Table 2) with the data of the fused quinazolinones **11a**−**c** and **14**, which are necessarily angular products. On the other hand, linear thiazolo(or 1,3-thiazino) quinazolinones **2**, **4** exhibit different UV maxima. Examples are outlined in Table 2. In particular, the absorbance between λ = 275−284 nm indicates the linear type, and the absence of a maximum in this range the angular isomer. Significant differences of the $^{13}C$ NMR signals could also be used to distinguish angular from linear regioisomers. The characteristic features of the angular compounds are the NMR shifts of C-9a carbons at lower field, as well as the C-3a and C-5 signals at higher field, compared to the linear thiazolo- or 1,3-thiazinoquinazolinones **2**, **4** (Table 2).[10] The angular structure of **8a** and **8d** could by concluded from their magnetic shifts. $^{13}C$ NMR signals of the aromatic CH carbons were assigned on the basis of $^{13}C/^{1}H$ correlation experiments. Thus, in angular compounds **8a**,**d**, **11a**−**c**, **14**, the low field signal in the range of 115−117 ppm was attributed to C-9, whereas in linear thiazolo or 1,3-thiazinoquinazolinones **2**, **4** all of the aromatic CH carbon resonances were observed at higher field.[3] The angular thiazolo structures **8a**, **8d** could be confirmed by $^{1}H$ nuclear Overhauser effect (Figure). In particular, in the case of **8a**, on irradiation of the 9-H resonance a NOE in 1-H was observed. In the case of **8d**, irradiation of the methyl resonance resulted in NOEs in 9-H as well as 2-$H^A$, the diastereotopic proton situated at the same face as the methyl group.

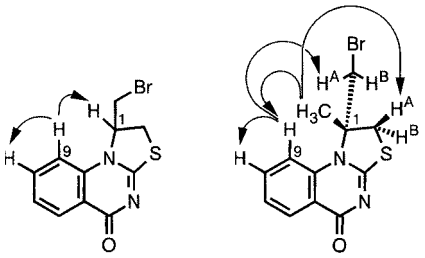


**Figure** Relevant NOE enhancements of **8a** and **8d**. Compound **8d** is shown as a single enantiomer

**Table 1** Compounds **7**−**14** Prepared

| Product | Yield (%) | mp (°C) (solvent) | IR (KBr) $\nu_{c=o}$ ($cm^{-1}$) | MS (70 eV) *m/z* (%) | UV (EtOH) $\lambda_{max}$ (nm) (log ε) | $^1$H NMR (DMSO-$d_6$/TMS) δ, *J* (Hz) | $^{13}$C NMR (DMSO-$d_6$/TMS) δ |
|---|---|---|---|---|---|---|---|
| **7d** | 91 | 168−170 (EtOH) | 1668 | 232 ($M^+$, 51) | 230 (4.48), 275 (4.23), 315 (3.82) | 1.86 (s, 3 H, $CH_3$), 3.99 (s, 2 H, $SCH_2$), 4.90 (s, 1 H, C=$CH_2$), 5.09 (s, 1 H, C=$CH_2$), 7.37−8.11 (m, 4 $H_{arom}$), 12.55 (s, 1 H, NH) | 21.10 ($CH_3$), 36.18 ($SCH_2$), 114.54 (C=*C*$H_2$), 119.96 (C-4a), 125.52, 125.77, 125.96 (C-5, C-6, C-8), 134.55 (C-7), 140.29 (*C*=$CH_2$), 148.25 (C-8a), 155.12 (C-2), 161.17 (C-4) |
| **7e** | 89 | 230−232 (EtOH) | 1650 | 266 ($M^+$, 100) | 274 (3.80), 318 (4.04) | 1.79 (s, 3 H, $CH_3$), 2.31 and 2.33 (2 s, 2 × 3 H, 5-$CH_3$ and 6-$CH_3$), 3.84 (s, 2 H, $SCH_2$), 4.88 (s, 1 H, C=$CH_2$), 5.03 (s, 1 H, C=$CH_2$), 12.54 (s, 1 H, NH) | 12.38, 12.70 (5-$CH_3$, 6-$CH_3$), 21.12 ($CH_3$), 36.39 ($SCH_2$), 114.65 (C=*C*$H_2$), 119.87 (C-4a), 127.39, 128.43 (C-5, C-6), 140.06 (*C*=$CH_2$), 154.90, 158.30 (C-2, C-7a), 161.67 (C-4) |
| **7f** | 92 | 214−216 (EtOH) | 1660 | 292 ($M^+$, 100) | 274 (3.80, 320 (4.08) | 1.68−1.74 (m, 4 H, $CH_2$), 1.78 (s, 3 H, $CH_3$), 2.65−2.85 (m, 4 H, $CH_2$), 3.85 (s, 2 H, $SCH_2$), 4.88 (s, 1 H, C=$CH_2$), 5.02 (s, 1 H, C=$CH_2$), 12.55 (s, 1 H, NH) | 21.11 ($CH_3$), 21.71, 22.47 (C-6, C-7), 24.28, 25.15 (C-5, C-8), 36.42 ($SCH_2$), 114.65 (C=*C*$H_2$), 119.05 (C-4a), 130.36, 130.56 (C-4b, C-8a), 140.07 (*C*=$CH_2$), 154.70, 158.07 (C-2, C-9a), 162.44 (C-4) |
| **8a** | 74 | 178−183 (EtOH) | 1706 | 298, 296 ($M^+$, 16), 203 ($M^+$ − $CH_2Br$, 56), 80, 82 (100) | 231 (4.11), 256 (4.15), 307 (3.60) | 3.66 (d, 1 H, *J* = 12.1, $CH_2$), 3.83 (dd, 1 H, *J* = 11.3, 2.6, $CH_2$), 3.91−4.09 (m, 2 H, $CH_2$), 5.78−5.86 (m, 1 H, CH), 7.51−7.58 (m, 1 H, H-7), 7.60−7.63 (m, 1 H, H-9), 7.85−7.92 (m, 1 H, H-8), 8.08−8.11 (m, 1 H, H-6) | 31.21, 31.61 ($CH_2Br$, C-2), 61.92 (C-1), 116.45 (C-9), 117.63 (C-5a), 126.38 (C-7), 127.96 (C-6), 135.04 (C-8), 137.64 (C-9a), 163.82, 168.61 (C-3a, C-5) |
| **8b** | 52 | 190−192 (MeOH) | 1636 | 332, 330 ($M^+$, 33), 250 ($M^+$ − HBr, 100) | 237 (4.30), 293 (4.01) | 2.34 (s, 6 H, $CH_3$), 3.50 (dd, 1 H, *J* = 12.0, 1.9, $CH_2$), 3.84−4.05 (m, 3 H, $CH_2$), 5.24−5.32 (m, 1 H, CH) | 12.08, 12.67 (6-$CH_3$, 7-$CH_3$), 30.62, 32.00 ($CH_2Br$, C-2), 63.49 (C-1), 119.24 (C-5a), 125.11, 130.18 (C-6, C-7), 145.84 (C-8a), 163.76, 164.30 (C-3a, C-5) |
| **8c** | 38 | 178−180 (MeCN) | 1632 | 358, 356 ($M^+$, 9), 276 ($M^+$ − HBr, 100) | 237 (4.33), 296 (4.07) | 1.62−1.83 (m, 4 H, $CH_2$), 2.66−2.88 (m, 4 H, $CH_2$), 3.50 (dd, 1 H, *J* = 11.8, 1.9, $CH_2$), 3.84−4.04 (m, 3 H, $CH_2$), 5.22−5.30 (m, 1 H, CH) | 21.57, 22.47 (C-7, C-8), 24.05, 25.25 (C-6, C-9), 30.60, 32.06 ($CH_2Br$, C-2), 63.52 (C-1), 118.54 (C-5a), 128.19, 132.24 (C-5b, C-9a), 146.40 (C-10a), 163.91, 164.16 (C-3a, C-5) |
| **8d** | 86 | 259 (dec.) (EtOH) | 1702 | 312, 310 ($M^+$, 28), 231 ($M^+$ − Br, 29), 217 ($M^+$ − $CH_2Br$, 100) | 232 (4.21), 256 (4.22), 307 (3.65) | 1.99 (s, 3 H, $CH_3$), 3.56 (d, 1 H, $J_{AB}$ = 12.2, 2-$H^A$), 3.74 (d, 1 H, $J_{AB}$ = 12.2, 2-$H^B$), 4.17 (d, 1 H, $J_{AB}$ = 11.8, CH*H*$^B$Br), 4.62 (d, 1 H, $J_{AB}$ = 11.8, C*H*$^A$HBr), 7.48−7.54 (m , 1 H, H-7), 7.73−7.80 (m, 1 H, H-8), 7.94−7.98 (m, 1 H, H-9), 8.10−8.14 (m, 1 H, H-6) | 23.48 ($CH_3$), 38.38, 38.79 ($CH_2Br$, C-2), 74.51 (C-1), 116.07 (C-9), 118.29 (C-5a), 126.90 (C-7), 128.52 (C-6), 135.19 (C-8), 137.66 (C-9a), 161.96, 169.22 (C-3a, C-5) |
| **8e** | 68 | 146−148 (MeOH/$H_2O$) | 1644 | 346, 344 ($M^+$, 19), 265 ($M^+$ − Br, 34), 80, 82 (100) | 236 (4.31), 293 (3.97) | 1.85 (s, 3 H, 1-$CH_3$), 2.34 (s, 6 H, 6-$CH_3$, 7-$CH_3$), 3.55 (d, 1 H, *J* = 12.1, $CH_2$), 3.72 (d, 1 H, *J* = 12.1, $CH_2$), 4.11 (d, 1 H, *J* = 12.1, $CH_2$), 4.24 (d, 1 H, *J* = 12.1, $CH_2$) | 11.83, 12.65 (6-$CH_3$, 7-$CH_3$), 21.94 (1-$CH_3$), 36.16, 37.32 ($CH_2Br$, C-2), 72.49 (C-1), 120.18 (C-5a), 124.82, 129.62 (C-6, C-7), 144.38 (C-8a), 163.57, 163.97 (C-3a, C-5) |

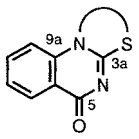
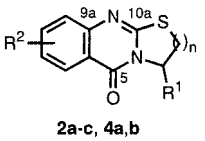
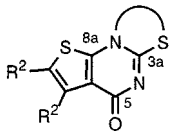
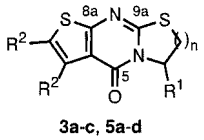
**Table 1** (continued)

| Product | Yield (%) | mp (°C) (solvent) | IR (KBr) $\nu_{c=o}$ ($cm^{-1}$) | MS (70 eV) *m/z* (%) | UV (EtOH) $\lambda_{max}$ (nm) (log ε) | $^1$H NMR (DMSO-$d_6$/TMS) δ, *J* (Hz) | $^{13}$C NMR (DMSO-$d_6$/TMS) δ |
|---|---|---|---|---|---|---|---|
| **8f** | 42 | 187−189 (MeCN) | 1638 | 372, 370 ($M^+$, 41), 291 ($M^+$ − Br, 100) | 237 (4.26), 296 (4.00) | 1.63-1.85 (m, 4 H, $CH_2$), 1.84 (s, 3 H, $CH_3$), 2.64−2.84 (m, 4 H, $CH_2$), 3.53 (d, 1 H, *J* = 12.0, $CH_2$), 3.71 (d, 1 H, *J* = 12.0, $CH_2$), 4.10 (d, 1 H, *J* = 12.1, $CH_2$), 4.24 (d, 1 H, *J* = 12.1, $CH_2$) | 21.59, 22.37 (C-7, C-8), 21.91 ($CH_3$), 23.73, 25.18 (C-6, C-9), 35.99, 37.39 ($CH_2$Br, C-2), 72.29 (C-1), 119.44 (C-5a), 127.65, 131.64 (C-5b, C-9a), 144.94 (C-10a), 163.77, 164.05 (C-3a, C-5) |
| **9a** | 79 | 88−92 (EtOH/ $H_2O$) | 1642 | − | − | 3.78−3.84 (m, 2 H, NHC*H*$_2$), 5.12−5.29 (m, 2 H, CH=C*H*$_2$), 5.85−6.05 (m, 1 H, CH), 6.51−7.65 (m, 5H$_{arom}$ and $CONH_2$), 7.86 (br s, 1 H, $CONH_2$), 8.31 (t, 1 H, *J* = 7.3 , NH) | 44.82 ($NHCH_2$), 111.68, 114.37, 129.30 (C-3, C-5, C-6), 114.27 (C-1), 115.58 (CH=*C*$H_2$), 132.77 (*C*H=$CH_2$), 135.89 (C-4), 149.91 (C-2), 171.96 ($CONH_2$) |
| **9b** | 87 | 130 (EtOH/ $H_2O$) | 1622 | 190 ($M^+$, 50), 132 (100) | − | 1.71 (s, 3 H, $CH_3$), 3.69 (d, 2 H, *J* = 5.8, NHC*H*$_2$), 4.82 (s, 1 H, C=$CH_2$), 4.86 (s, 1 H, C=$CH_2$), 6.51−7.63 (m, 4 H$_{arom}$), 7.14 (s, 1 H, $CONH_2$), 7.84 (s, 1 H, $CONH_2$), 8.39 (t, 1 H, *J* = 5.8, NH) | 20.13 ($CH_3$), 47.93 ($NHCH_2$), 109.99 (C=*C*$H_2$), 113.82 (C-1), 111.45, 113.98, 128.98 (C-3, C-5, C-6), 132.39 (C-4), 142.50 (*C*=$CH_2$), 149.80 (C-2), 171.67 ($CONH_2$) |
| **9c** | 83 | 118−121 (EtOH/ $H_2O$) | 1666 | 190 ($M^+$, 88), 77 (100) | − | 1.66 (d, 3 H, *J* = 11.6, $CH_3$), 3.69−3.73 (m, 2 H, $NHCH_2$), 5.59−5.66 (m, 2 H, CH=CH), 6.49−7.64 (m, 4 H$_{arom}$), 7.14 (s, 1 H, $CONH_2$), 7.81 (s, 1 H, $CONH_2$), 8.18 (br s, 1 H, NH) | 17.77 ($CH_3$), 44.22 ($NHCH_2$), 111.55, 114.10, 128.91 (C-3, C-5, C-6), 114.06 (C-1), 132.69 (C-4), 126.62 (*C*H=CH), 129.18 (CH=*C*H), 149.90 (C-2), 171.93 ($CONH_2$) |
| **10a** | 49 | 179−180 (EtOH) | 1692 | 218 ($M^+$, 27), 203 (100) | − | 5.09−5.23 (m, 2 H, CH=C*H*$_2$), 5.33−5.40 (m, 2 H, $NCH_2$), 5.86−6.00 (m, 1 H, C*H*=$CH_2$), 7.37−8.07 (m, 4 H$_{arom}$), 12.71 (s, 1 H, NH) | 50.39 ($NCH_2$), 116.79, 124.56, 127.30 (C-5, C-6, C-8), 135.46 (C-7), 117.12 (CH=*C*$H_2$), 117.94 (C-4a), 131.18 (*C*H=$CH_2$), 140.60 (C-8a), 158.24 (C-4), 175.84 (C-2) |
| **10b** | 53 | 181−182 (EtOH) | 1682 | 232 ($M^+$, 31), 217 (100) | − | 1.80 (s, 3 H, $CH_3$), 4.46 (s, 1 H, C=$CH_2$), 4.86 (s, 1 H, C=$CH_2$), 5.11-5.18 (m, 2H, $NCH_2$), 7.33−8.07 (m, 4 H$_{arom}$), 12.72 (s, 1 H, NH) | 19.86 ($CH_3$), 53.20 ($NCH_2$), 110.36 (C=*C*$H_2$), 116.90, 124.58, 127.18 (C-5, C-6, C-8), 117.70 (C-4a), 135.43 (C-7), 138.08 (*C*=$CH_2$), 140.77 (C-8a), 158.22 (C-4), 176.13 (C-2) |
| **10c** | 47 | 199−202 (EtOH) | 1684 | 232 ($M^+$, 25), 203 (100) | − | 1.63 (dd, 3 H, *J* = 6.9, 1.1, $CH_3$), 5.23−5.33 (m, 2 H, $NCH_2$), 5.50−5.62 (m, 1 H, CH=C*H*$CH_3$), 5.67−5.78 (m, 1 H, C*H*=$CHCH_3$), 7.35−8.07 (m, 4 H$_{arom}$), 12.67 (s, 1 H, NH) | 17.51 ($CH_3$), 49.69 ($NCH_2$), 116.71, 124.53, 127.32 (C-5, C-6, C-8), 117.98 (C-4a), 123.87, 128.75 (CH=*C*H$CH_3$, *C*H=$CHCH_3$), 135.51 (C-7), 140.62 (C-8a), 158.21 (C-4), 175.60 (C-2) |
| **11a** | 62 | 241 (dec.) (MeOH) | 1700 | 298, 296 ($M^+$, 5), 216 ($M^+$ − HBr, 38), 80, 82 (100) | 237 (4.14), 252 (4.22), 309 (3.67) | 3.98 (d, 2 H, *J* = 5.9, $CH_2$Br), 4.70−4.80 (m, 1 H, CH), 4.80−4.82 (m, 2 H, $NCH_2$), 7.62−8.13 (m, 4 H$_{arom}$) | 35.57 ($CH_2$Br), 45.26 (C-2), 55.05 (C-1), 117.28 (C-9), 117.72 (C-5a), 127.22, 127.63 (C-6, C-7), 135.85 (C-8), 138.40 (C-9a), 161.15, 166.63 (C-3a, C-5) |
| **11b** | 69 | 223−226 (MeOH) | 1720 | 312, 310 ($M^+$, 65), 231 ($M^+$ − Br, 55), 230 ($M^+$ − HBr, 62), 80, 82 (100) | 236 (4.28), 252 (4.30), 310 (3.77) | 1.82 (s, 3 H, $CH_3$), 4.11 (d, 1 H, *J* = 7.7, $CH_2$Br), 4.17 (d, 1 H, *J* = 7.7, $CH_2$Br), 4.54 (d, 1 H, *J* = 11.8, $NCH_2$), 4.78 (d, 1H , *J* = 11.8, $NCH_2$), 7.55−8.11 (m, 4 H$_{arom}$) | 24.69 ($CH_3$), 41.66 ($CH_2$Br), 54.31 (C-1), 59.50 (C-2), 116.47 (C-9), 117.79 (C-5a), 126.24, 127.59 (C-6, C-7), 134.83 (C-8), 138.96 (C-9a), 164.06, 166.84 (C-3a, C-5) |

**Table 1** (continued)

| Product | Yield (%) | mp (°C) (solvent) | IR (KBr) $\nu_{c=o}$ ($cm^{-1}$) | MS (70 eV) *m/z* (%) | UV (EtOH) $\lambda_{max}$ (nm) (log ε) | $^1$H NMR (DMSO-$d_6$/TMS) δ, *J* (Hz) | $^{13}$C NMR (DMSO-$d_6$/TMS) δ |
|---|---|---|---|---|---|---|---|
| **11c** | 61 | 290 (dec.) (EtOH) | 1698 | 312, 310 ($M^+$, 7), 230 ($M^+$ − HBr, 23), 80, 82 (100) | 237 (4.57), 252 (4.34), 309 (3.77) | 1.78 (d, 3 H, *J* = 6.3, $CH_3$), 4.76−4.91 (m, 4 H, $NCH_2$ and $NCH_2CHCH$Br), 7.60−8.14 (m, 4 $H_{arom}$) | 22.87 ($CH_3$), 50.54 (C-2), 52.90 (CHBr), 54.50 (C-1), 117.23 (C-9), 117.64 (C-5a), 127.20, 127.67 (C-6, C-7), 135.76 (C-8), 138.15 (C-9a), 161.44, 166.58 (C-3a, C-5) |
| **12** | 76 | 114−115 (EtOH) | 1622 | 190 ($M^+$, 15), 132 (100) | − | 2.25−2.40 (m. 2 H, $NHCH_2CH_2$), 3.09−3.23 (m, 2 H, $NHCH_2$), 5.04−5.17 (m, 2 H, $CH=CH_2$), 5.55−5.95 (m, 1 H, $CH=CH_2$) 6.49−7.61 (m, 4 $H_{arom}$), 7.09 (s, 1 H, $CONH_2$), 7.77 (s, 1 H, $CONH_2$), 8.13 (t, 1 H, NH) | 33.01 ($NHCH_2CH_2$), 41.52 ($NHCH_2$), 110.98, 113.78, 129.01 (C-3, C-5, C-6), 113.83 (C-1), 116.72 ($CH=CH_2$), 132.56 ($CH=CH_2$), 135.99 (C-4), 149.66 (C-2), 171.56 ($CONH_2$) |
| **13** | 39 | 184−185 (EtOH) | 1682 | 232 ($M^+$, 25), 203 (74), 120 (100) | − | 2.43-2.53 (m, 2 H, $NCH_2CH_2$), 4.60−4.82 (m, 2 H, $NCH_2$), 5.04−5.20 (m, 2 H, $CH=CH_2$), 5.86−6.00 (m, 1 H, $CH=CH_2$), 7.36−8.20 (m, 4 $H_{arom}$), 12.63 (s, 1 H, NH) | 30.25 ($NCH_2CH_2$), 47.22 ($NCH_2$), 116.18, 124.49, 127.44 (C-5, C-6, C-8), 117.32 ($CH=CH_2$), 117.93 (C-4a), 134.23 ($CH=CH_2$), 135.68 (C-7), 140.42 (C-8a), 158.11 (C-4), 175.35 (C-2) |
| **14** | 86 | 205 (MeOH) | 1696 | 312, 310 ($M^+$, 28), 230 ($M^+$ − HBr, 100) | 230 (4.34), 256 (4.48), 301 (4.09) | 2.25−2.40 (m, 1 H), 2.45−2.61 (m, 2 H), 3.84−3.98 (m, 2H), 4.21−4.38 (m, 2 H), 7.46−8.06 (m, 4 $H_{arom}$) | 26.57 (C-2), 35.23 ($CH_2Br$), 41.43 (C-3), 43.31 (C-1), 114.89 (C-10), 119.59 (C-6a), 125.66, 127.22 (C-7, C-8), 133.48 (C-9), 141.67 (C-10a), 161.68, 164.88 (C-4a, C-6) |

**Table 2** Characteristic $^{13}$C NMR Chemical Shifts[a] and UV Data of Angular and Linear[b,c,d] Thiazolo(1,3-thiazino)quinazolinones and Thienopyrimidinones

| Spectra Recorded |  **8a,d, 11a-c, 14** | |  **2a-c, 4a,b** | |  **8b,c,e,f** | |  **3a-c, 5a-d** | |
|---|---|---|---|---|---|---|---|---|
| $^{13}$C NMR | C-9a | 137.6−141.7 | C-9a | 146.9−148.5 | C-8a | 144.4−146.4 | C-9a, C-8a | 154.1−160.0 |
| (DMSO-$d_6$/TMS) δ | C-3a, C-5 | 161.2−169.2 | C-10a | 153.6−159.5 | C-3a, C-5 | 163.8−164.3 | C-5 | 160.1−162.6 |
| | | | C-5 | 159.2−160.5 | | | | |
| UV (EtOH) | 230−237, | | 235−237, | | 236−237, | | 276−281, | |
| $\lambda_{max}$ (nm) | 252−256, | | 275−284, | | 293−296 | | 320−331 | |
| | 301−310 | | 312−326[e] | | | | | |

[a] Atomic numbering refers to tricyclic thiazolo compounds.
[b] Data[3,14] of the following compounds **2**, **4** were considered; **2a**: n = 1, $R^1 = R^2 = H$; **2b**: n = 1, $R^1$ = Me, $R^2$ = H; **2c**: n = 1, $R^1$ = Et, $R^2$ = H; **4a**: n = 2, $R^1 = R^2 = H$; **4b**: n = 2, $R^1$ = Me, $R^2$ = H.
[c] Data[3,19] of the following compounds **3**, **5** were considered; **3a**: n = 1, $R^1$ = H, $R^2R^2 = (CH_2)_4$; **3b**: n =1, $R^1 = R^2$ = Me; **3c**: n = 1, $R^1$ = Me, $R^2R^2 = (CH_2)_4$; **5a**: n = 2, $R^1$ = H, $R^2$ = Me; **5b**: n = 2, $R^1$ = H, $R^2R^2 = (CH_2)_4$; **5c**: n = 2, $R^1 = R^2$ = Me; **5d**: n = 2, $R^1$ = Me, $R^2R^2 = (CH_2)_4$.
[d] The complete $^{13}$C NMR data unless already published are given in the text.
[e] In some compounds as shoulder.

Similar results on bromination-cyclization reactions of monocyclic 2-(allylthio)pyrimidin-4-ones have been published recently by Danel et al.[5] Prior to the addition of bromine, the substrates were treated with *N*,*O*-bis(trimethylsilyl)acetamide. After column chromatographic purification, corresponding N-1 cyclized 3-(bromomethyl)thiazolo[3,2-*a*]pyrimidin-7-ones were obtained in moderate yields. In the present quinazolinone series, regioselective cyclization was achieved without silylation to form the tricyclic products **8a** and **8d** in 74% and 86% yields, respectively. Chromatographic purification was not nessecary.

Regioselective cyclization to angular, 5-membered rings was also achieved with 2-(alkenylthio)thieno[2,3-*d*]pyrimidin-4-ones **7b**,**c**,**e**,**f** as substrates. The corresponding products **8** were obtained only in moderate yields, since the main products had to be purified by fractional crystallization. Again, structural elucidation of the thiophene derived products was based on characteristic features to distinguish angular from linear structures (Table 2). Comparison of the UV and $^{13}C$ NMR data of **8b**,**c**,**e**,**f** with those of the linear reference compounds **3**, **5** unequivocally indicated their angular structure.

Angular anellation was structurally forced in the route to the tricyclic compounds **11** and **14**. The final bromocyclization was found to be selective with respect to the formation of the five-membered (**11**) or six-membered (**14**) regioisomers, which were obtained in 61−86% yields.

Whereas 2-alkenylthio derivatives were found to undergo a regioselective cyclization[3] to the corresponding linear products **2**−**5** upon treatment with concentrated sulfuric acid (Scheme 1), in the present transformation (Scheme 2) angular products were formed. Likely, this difference is attributed to protonation of the N-1 in the former case, leading to an intramolecular alkylation of the lactam nitrogen. In the present conversion, intramolecular alkylation of the more nucleophilic, non-protonated N-1 atom provided cyclization to the final products. Their structures are in accordance with the tendency for preferential formation of a five-membered (compared to six-membered) ring (**8**, **11**), as well as the favoured formation of a six-membered (compared to seven-membered) ring (**14**). Probably, the ring-closure to **8**, **11**, **14** involves direct nucleophilic attack of the N-1 or S atom at an intermediate carbocation[12] or bromonium ion respectively.[13] However, dibromo addition on the side chain followed by intramolecular nucleophilic attack of the N-1, or S atom at the corresponding bromosubstituted carbon might also be operative.

Previously, Chern et al.[11] have reported on the transformation of 2-(allylthio)quinazolin-4(3*H*)-one **7a** with *N*-bromosuccinimide in THF to the linear 3-(bromomethyl)-5*H*-thiazolo[2,3-*b*]quinazolin-5-one **2** (n = 1, $R^1 = CH_2Br$, $R^2$ = H; Table 2). Following the reported procedure, we have obtained a product (mp 177−179 °C, instead of the reported value 235−237 °C), which was identical with the angular **8a**, prepared from **7a** and bromine in acetic acid.

In summary, a convenient bromination-cyclization reaction of various alkenyl substituted substrates was found to result in a regioselective cyclization to bromomethyl substituted 5*H*-thiazolo[3,2-*a*]quinazolin-5-ones and analogous 5*H*-thieno[3,2-*e*]thiazolo[3,2-*a*]pyrimidin-5-ones. These methodologies allows one a ready access to such heterocycles which may find applications as bioactive compounds as well as useful intermediates for further transformations.

Melting points were determined on a Boetius apparatus and are not corrected. IR spectra were measured with a Perkin Elmer 16 PC FTIR spectrometer. Mass spectra (70 eV) were obtained using a Varian MAT CH6 spectrometer. UV spectra were recorded on a Shimadzu UV-VIS spectrophotometer UV-160A. $^1H$ NMR spectra (300 MHz) and $^{13}C$ NMR spectra (75 MHz) were recorded on a Varian Gemini 300. TLC was performed on Merck aluminum sheets, silica gel 60 $F_{254}$. Satisfactory elemental analyses were obtained for all new compounds: C ± 0.36, H ± 0.38, N ± 0.41.

Compounds **6**[15−17] and **7a**−**c**[3] were synthesized as reported. 2-Methallylthio derivatives **7d**−**f** (Table 1) were prepared from the corresponding 2-thioxo derivative **6** and 3-chloro-2-methylpropene according to a reported procedure.[3] Angular thiazolo(1,3-thiazino) quinazolinones **2**, **4**[3,15,18] and thienopyrimidinones **3**, **5**[3,19] (Table 2) were prepared as reported.

Some unpublished spectral data of **2**−**5** are given below:

**2,3-Dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (2a)**
$^{13}C$ NMR (DMSO-$d_6$): δ = 26.04 (C-2), 48.32 (C-3), 118.72 (C-5a), 125.62, 125.94 (C-6, 7, 9), 134.46 (C-8), 148.54 (C-9a), 159.51 (C-10a), 160.27 (C-5).

**2,3,6,7,8,9-Hexahydro-5*H*-[1]benzothieno[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one (3a)**
$^{13}C$ NMR (DMSO-$d_6$): δ = 21.70, 22.44, 24.35, 25.13 ($CH_2$), 26.70 (C-2), 48.17 (C-3), 118.08 (C-5a), 130.34, 130.75 (C-5b, 9a), 156.39, 160.00 (C-11a, 10a), 162.62 (C-5).

**3,4-Dihydro-2*H*,6*H*-[1,3]thiazino[2,3-*b*]quinazolin-6-one (4a)**
$^{13}C$ NMR (DMSO-$d_6$): δ = 22.40 (C-3), 27.18 (C-2), 41.66 (C-4), 118.95 (C-6a), 125.23, 125.27, 126.34 (C-7, 8, 10), 134.55 (C-9), 146.95 (C-10a), 154.48 (C-11a), 160.53 (C-6).

**2,3-Dimethyl-7,8-dihydro-4*H*,6*H*-thieno[2',3':4,5]pyrimido-[2,1-*b*][1,3]thiazin-4-one (5a)**
$^{13}C$ NMR (DMSO-$d_6$): δ = 12.49, 12.80 (2-$CH_3$, 3-$CH_3$), 22.43 (C-7), 27.18 (C-8), 40.96 (C-6), 118.84 (C-3a), 127.11, 128.34 (C-2, 3), 154.14, 157.45 (C-9a, 10a), 160.34 (C-4).

**3,4,7,8,9,10-Hexahydro-2*H*,6*H*-[1]benzothieno[2',3':4,5]pyrimido[2,1-*b*][1,3]thiazin-6-one (5b)**
$^{13}C$ NMR (DMSO-$d_6$): δ = 21.74, 22.45, 24.36, 25.21 ($CH_2$), 22.39 (C-3), 27.24 (C-2), 40.90 (C-4), 117.99 (C-6a), 130.12, 130.50 (C-6b, 10a), 154.26, 157,18 (C-12a, 11a), 160.10 (C-6).

**2-(Alkenylamino)benzamides 9a-c, 12; General Procedure**
A mixture of 2-aminobenzamide (13.6 g, 100 mmmol) and $K_2CO_3$ (6.9 g, 50 mmol) was suspended in $H_2O$ (80 mL). The appropriate alkenyl halide (allyl chloride, 3-chloro-2-methylpropene, crotyl chloride,[20] or 4-bromobut-1-ene, respectively, each 100 mmol) was added and the mixture was refluxed. The reaction was monitored by TLC. After completion, the mixture was cooled and the precipitate was collected by filtration. Oily products were mixed with a small amount of EtOH to obtain a solid. The crude product was recrystallized as indicated (Table 1).

**1-Alkenyl-2-thioxo-1*H*-quinazolin-4(3*H*)-ones 10a−c, 13; General Procedure**

The corresponding 2-(alkenylamino)benzamide **9a**−**c**, **12** (50 mmol) was dissolved in acetone (50 mL) and treated with a freshly prepared solution of benzoyl isothiocyanate[21] (19.56 g, 120 mmol) in acetone (60 mL). The mixture was stirred at r.t. for 24 h. Aq 3 N NaOH was added to obtain pH 9. The mixture was heated to 60 °C and the insoluble material was removed by filtration. The filtrate was acidified with 3 N HCl to pH 2, the mixture was cooled, the precipitate was collected by filtration and washed with $H_2O$. The crude product was recrystallized as indicated (Table 1).

**1,2-Dihydro-5*H*-thiazolo[3,2-*a*]quinazolin-5-ones 8a, 8d, 11a−c and 3-(Bromomethyl)-2,3-dihydro-1*H*,6*H*-[1,3]thiazino[3,2-*a*]quinazolin-6-one (14); General Procedure**

The corresponding 2-(alkenylthio)quinazolin-4-one **7a,d** or 1-alkenyl-2-thioxoquinazolin-4-one **10 a−e** and **13** (10 mmol) was suspended in 95% AcOH (40 mL). The mixture was cooled to 7 °C and stirred. A solution of $Br_2$ (1.76 g, 11 mmol) in glacial AcOH (11 mL) was added dropwise over 30 min. The temperature of the mixture was kept below 10 °C. Stirring was then continued and the temperature was slowly increased to 40 °C. The precipitate was collected by filtration, washed with $H_2O$, suspended in $NaHCO_3$ solution, and filtered off. The crude product was recrystallized as indicated (Table 1).

**1,2-Dihydro-5*H*-thieno[3,2-*e*]thiazolo[3,2-*a*]pyrimidin-5-ones 8b, 8e and 1,2,6,7,8,9-hexahydro-5*H*-[1]benzothieno[3,2-*e*]thiazolo[3,2-*a*]pyrimidin-5-ones 8c, 8f; General Procedure**

The corresponding 2-(alkenylthio)thieno[2,3-*d*]pyrimidin-4-one **7b, c,e,f** (10 mmol) was suspended in 95% AcOH (200 mL). At 7 °C, a solution of $Br_2$ (2.4 g, 15 mmol) in glacial AcOH (15 mL) was added dropwise over 30 min to the stirred mixture. The temperature was allowed to reach 40 °C. The mixture was then cooled again, and the precipitate was collected by filtration, washed with ice-water, $NaHCO_3$ solution, and $H_2O$. Further product was obtained by pouring the filtrate onto ice-water (200 mL) and collecting the precipitate by filtration. This material was washed with aq $NaHCO_3$ solution, $H_2O$, and dried. It was then suspended in boiling cyclohexane (100 mL), stirred for 2 min, and filtered off. The combined crude product was purified by fractional crystallization from the indicated solvent (Table 1).

## References


(1) For synthetic routes to tricyclic thiazolo(1,3-thiazino) pyrimidinones, see Ref. 3 and references therein. For a review on thiazolo(1,3-thiazino)quinazolines, see Ref. 4.

(2) For thiazolo[3,2-*a*]pyrimidinones, see Ref. 5, for thiazolo[2,3-*b*]quinazolinones, see Ref. 3 and references therein.

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(9) UV and $^{13}C$ NMR data of alkenylthio derivatives **7** were similar to those of the linear compounds **2**-**5** (Table 2), indicating the tautomeric 3*H*-pyrimidin-4-one structure.

(10) Similar differences in the $^{13}C$ NMR shifts have been considered to distinguish between angular and linear thiazolopyrimidinones, as well as thiazolo[1,2,4]benzothiadiazine 5,5-dioxides, see Refs 5, 11.

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(12) Cyclization of 2-(allylthio)pyrimidin-4(3*H*)-ones with bromine in $CH_2Cl_2$ was assumed to occur via electrophilic attack of the intermediate carbocation at N-1 atom, see Ref 5. Following this mechanism, in the present transformations a direct attack of the stabilized secondary (formed from **7a**−**c**, **10a**) or tertiary carbocation (from **7d**−**f**, **10b**) at the N-1 or S, respectively, would provide the thiazolo products **8**, **11**. The formation of the six-membered 1,3-thiazine ring in **14** could be explained accordingly.

(13) From the NMR data of **11c**, the purified compound appears as one of two possible diastereomers. Its predominant formation might be explained by assuming a bromonium ion intermediate and *anti* addition of the sulfur atom which gives the racemic (2*R*,1'*S*), (2*S*,1'*R*) pair.

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(20) Crotyl chloride (Merck) containing 90% of the *trans* isomer was used.

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