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Tetrahedron 62 (2006) 6398–6404
Tetrahedron

Access to substituted thiapyrrolizidinones and fused pyridones using the domino *N*-acyliminium-thionium equilibrium/1,3-dipolar cycloaddition/desulfurization cyclization cascade

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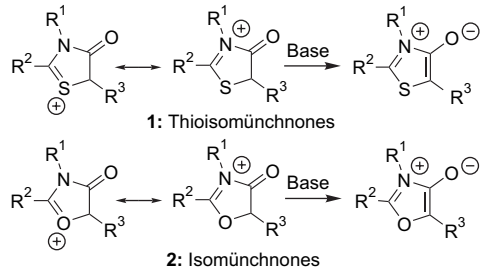
Received 10 March 2006; revised 5 April 2006; accepted 6 April 2006
Available online 6 May 2006

Abstract—Substituted thiapyrrolizidinones and fused pyridones, and quinolizinones were reported efficaciously from suitable thioamides in yields ranging from 30% to 65%. The reaction proceeded in a one-pot procedure as cascade process by the intramolecular 1,3-dipolar cycloaddition of thioisomünchnones followed by desulfurization of the adducts. During these investigations, the mechanistic aspects of the process were also discussed.

1. Introduction

Thioisomünchnones conventionally named 1,3-thiazolium-4-olates (**1**) and belonging to a five-membered mesoionic systems are receiving less attention compared to their oxygen homologues as isomünchnones (1,3-oxazolium-4-olates (**2**)), (Scheme 1).[1] Since the pioneering work by Potts and co-workers given on their syntheses and reactivity,[2] it has been demonstrated now that these species constitute powerful intermediates in the synthesis of complex nitrogen-containing heterocycles.[3] In particular, they offer rapid access to different heterocyclic compounds containing a pyridone nucleus useful in natural products syntheses[4] as well as β-lactams, polyhydrothiophenes in chiral form or not, thiiranes, thiophenes, etc.[4,5]



Scheme 1. Mesoionic five-membered heterocyclic mesomeric betaines.

These mesoionic ring systems, which are easily prepared by the reaction of *N*-monosubstituted thioamides with α-haloacyl halides in the presence of 2 equiv of triethylamine are stabilized by the conjugation effect as shown in Scheme 1 (thionium ion ↔ *N*-acylimiunim cation ↔ mesoionic specie). In addition, some extra stabilization could arise from the conjugation with an exocyclic electron rich aromatic or heteroaromatic system when R^2 is an aryl or heteroaryl group. As a consequence, these mesomeric betaines exhibit an interesting synthetic potential, which could be attributed in addition to (a) the interesting physical properties they possess,[6] and importantly (b) the propensity of its thio-carbonyl ylide dipole to undergo 1,3-dipolar cycloaddition with a range of double and triple-bond dipolarophiles.

Due to the high number of natural and unnatural biological active molecules containing the thiapyrrolizinone[7] and quinolizinone[8] subunits, the use of that approach is still of continuous interest in organic synthetic chemistry. Among the most known naturally occurring alkaloids, oxogambirtannine (**3**)[9] and sempervilam (**4**)[10] belonging to the yohimboid alkaloids, constitute one of the major subgroups of the indole class. If these structures have not yet shown any biological properties, mitragynaline (**5a**, R=OMe) as an indole alkaloid,[11] was isolated from the Malaysian *Mitragyna speciosa korth* plant. This is used in the Malay Peninsula as a stimulant like coca or as substitute from opium.[12] Moreover other tricyclic benzo- and thieno[*a*]quinazolines developed by investigators at Hoffman La-Roche, Ltd have been shown to be excellent alternatives to molecules with benzodiazepines scaffolds for the treatment of anxiety and sleep disorders.[13]

Keywords: Thioisomünchnone; 1,3-Dipolar cycloaddition; Thioamide; Heterocycle; Domino process; Lawesson's; Thionation; One-pot procedure.
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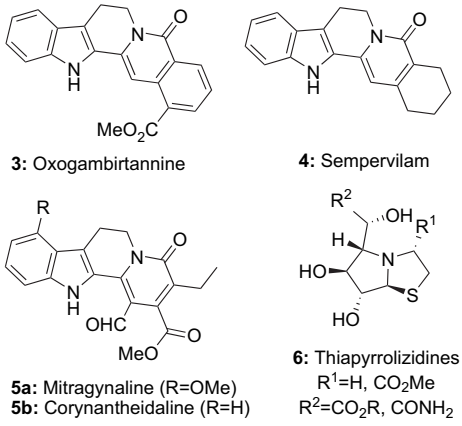
0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.04.032

On the other hand, pyrrolo[2,1-*b*]thiazoles are rare scaffolds since only few reports are done in the literature. In this sense, whatever, two related structures were reported by the Padwa group using that strategy[4,14] while others described some thia-analogues of the glycosidase inhibitors polyhydroxylated pyrrolizidinones (**6**, R^1=H and CO_2Me; R^2=CO_2R and $CONH_2$).[15,16] The strategy used in these cases was based on the cyclodehydration of thiazolidines bearing an hydroxymethyl branched group[15] and an unexpected ring contraction of 7,5-fused bicyclic thiazolidine-lactams,[16] respectively.

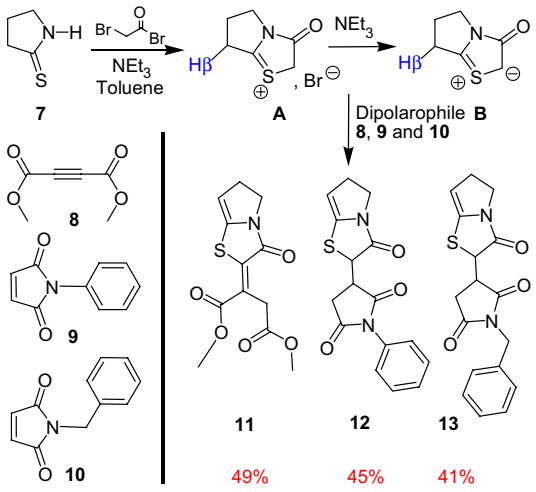
2. Results and discussion

As part of a long-term project dealing with our search for a simple synthetic route to heterocyclic homologues of the above structures (Scheme 2), which could be applicable to the synthesis of different condensed five and six-membered azacycles, we explore in this paper the intramolecular 1,3-dipolar cycloaddition of new thioisomünchnones with systematically three different dipolarophiles. This process proceeds in a one-pot procedure and result in the formation of new substituted 1,3-thiazolidinones and fused pyridones, heterocyclic scaffolds with promising biological activity.



Scheme 2. Representative structures containing thiapyrrolizinone and quinolizinone subunits.

Because of the use of thioisomünchnone of type **B** as a dipole, in cycloaddition reactions remains unreported, we first investigated the behavior of this thioisomünchnone, derived from pyrrolidine-2-thione (**7**), in the intramolecular 1,3-dipolar cycloaddition conditions as shown in Scheme 3. For this purpose, the requisite pyrrolidine-2-thione (**7**) was obtained in one step in quantitative yield by thionation of pyrrolidine-2-one with 1 equiv of Lawesson's reagent in dry toluene at reflux for 3 h[17] and the dipolarophile chosen as the reaction partner for optimizing conditions was the methyl acetylenedicarboxylate (**8**). So, after intensive screening of reaction conditions,[18] the use of 1.1 equiv of 2-bromoacetyl bromide, 2.0 equiv of dry triethylamine as a base, 1.5 equiv of suitable dipolarophile, and anhydrous toluene as solvent was found to be the most effective combination for obtaining representative results. Under these conditions, pyrrolidine-2-thione (**7**) with 2-bromoacetyl bromide and triethylamine led to thionium salt **A** then mesoionic five-membered **B**, which after reaction with dipolarophile **9**, led to the structure containing thiapyrrolizin-one ring **11** in 49% yield (Scheme 3).

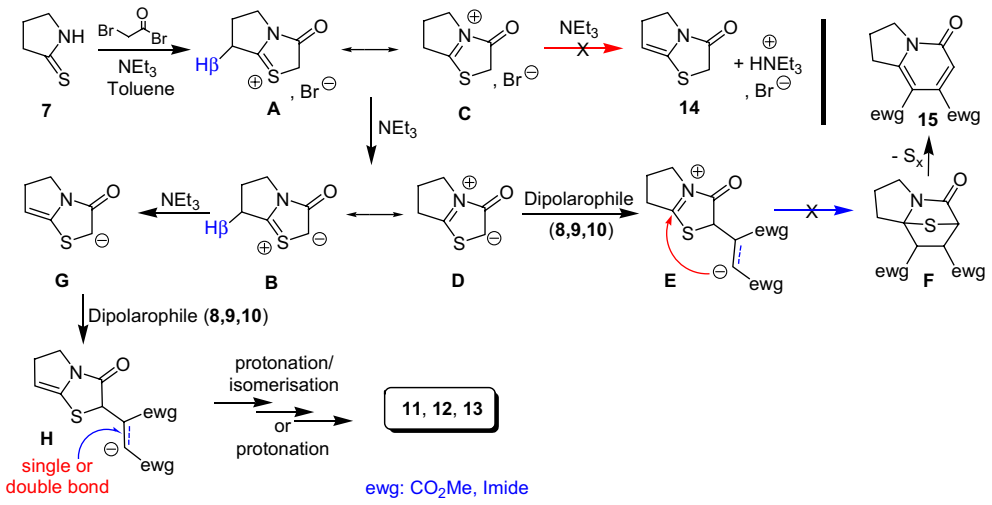


Scheme 3. Scheme leading to new structures containing thiapyrrolizinone nucleus as **11**, **12**, and **13** from betaine **B**.

Having the best conditions in hand, we examined next the reaction of the same substrate as above with 2-bromoacetyl bromide and other dipolarophiles in the presence of triethylamine (Scheme 3). In this context, the commercially available *N*-phenylmaleimide (**10**) and *N*-benzylmaleimide (**11**) were found to be employable efficaciously without the change of the course of the cascade process as well as the reaction yields. Indeed, the reaction products, identified as thiapyrrolizinones **12** and **13**, were isolated in 45% and 41% yields, respectively, comparables to that obtained for the thiapyrrolizinone derivative **11**.

As shown in Scheme 4, the suggested reaction mechanism illustrates three pathways that appear possible. Initially formed thionium cation **A**, in equilibrium with corresponding *N*-acyliminium one **C**, would lead with triethylamine to either the thiapyrrolizinone **14** or the carbanion **G** via mesoionic five-membered heterocyclic mesomeric betaines **B** and **D**, in equilibrium. No traces of product **14** were found in the reaction mixture examined by TLC before addition of a second equivalent of triethylamine, a dipolarophile as well as at the end of the reaction process before any purification. Also, no trace of pyridone component **15** as well as corresponding thia-bridged products **F**, which would be formed by the intramolecular 1,3-dipolar cycloaddition of 3-thiazolium-4-olate salt (**B** or **D**, see Scheme 4), was observed. Therefore, these thioisomünchnones species afforded the thiapyrrolizinones **11**, **12**, and **13** upon abstraction of the hydrogen atom at β-position of nitrogen and/or sulfur atom(s) in the intermediate (**A**↔**C**) or (**B**↔**D**) followed in an ultimate stage by addition of a dipolarophile and protonation of the resulting carbanion. Interestingly, the process seems to be general and the key step seems to be the hydrogen abstraction.

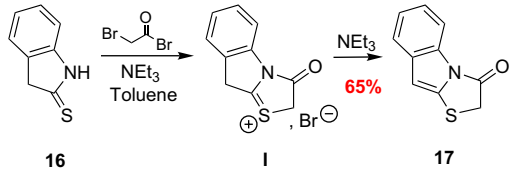
The ^{1}H NMR spectra of thiapyrrolizinones **11**, **12**, and **13** are characterized by having the olefinic proton of the dihydropyrrole nucleus in the aromatic region (from δ=6.98 up to 7.35 ppm). This was coupled with methylene protons at β-position of the dihydropyrrole ring and in the case of



Scheme 4. Mechanistic considerations leading to the formation of substituted thiapyrrolizinone scaffolds **11**, **12**, and **13**.

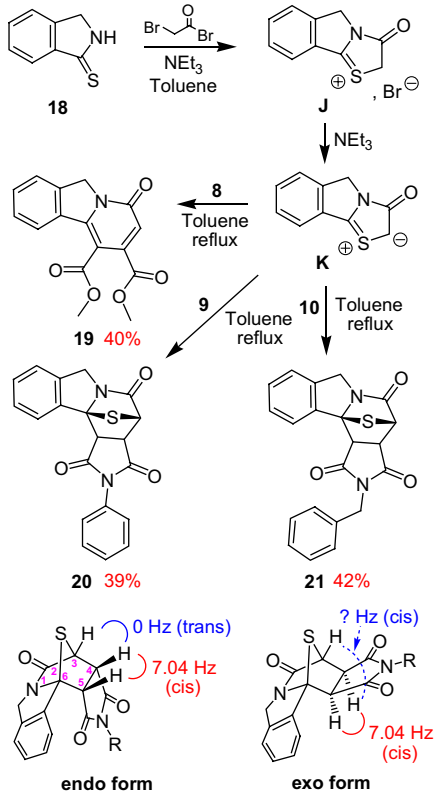
product **11**, they appear as a triplet at δ=6.98 ppm with coupling constant of J=5.48 Hz. This proton became singlet when the methylene protons outlined above were irradiated. Also, the ^{1}H NMR spectra of **11** showed the presence of three methylene groups CH_2 demonstrating the carbon–carbon double-bond migration. As a consequence, the resulting thiapyrrolizinone system bearing an exocyclic double-bond in the conjugation with either the sulfur atom or the carbonyl function constitutes the thermodynamic isomer.

Consistent with the above remark, isoindoline-1-thione (**16**) (Scheme 5), obtained from oxindole by known procedure[19] was subjected to our standard protocol outlined above. Surprisingly, whatever change operated in the experimental procedure only product namely, thiazolo[3,2-*a*]indol-3-one (**17**), was obtained as the sole reaction product in yields near 65%.[20] Also, when the reaction was repeated using more than 2 equiv of triethylamine (up to 4 equiv), the reaction profile remains unchanged. The change of dipolarophile in combination of an excess of triethylamine had also little effect on the course of the reaction as well as on the yield of the cyclized product **17**. From these considerations, the benzylic proton abstraction leading to the more stable fused indole **17** appears to be largely responsible for the differences observed in the formation of heterocyclic systems **11**, **12**, **13**, and **17**, respectively.[21]



Scheme 5. One-pot protocol leading to thiazolo[3,2-*a*]indol-3-one (**17**).

We next directed our attention to explore the behavior of 2,3-dihydroisoindole-1-thione (**18**)[22] under the precedent well established protocol. The choice of this thioamide is due to the absence of a proton at α-position of the thio-carbonyl function. Thus, treatment of **18** in the presence of 1 equiv of methyl acetylenedicarboxylate (**9**) according to conditions outlined above, gave exclusively after chromatography purification methyl 4-oxo-4,6-dihydropyrido[2,1-*a*]isoindole-1,2-dicarboxylate (**19**) as a brown solid in 40% yield (Scheme 6).



Scheme 6. One-pot procedure leading to dihydropyrido[2,1-*a*]isoindole **19** and thiadiazacyclopenta[*c*]fluorenetriones **20** and **21**.

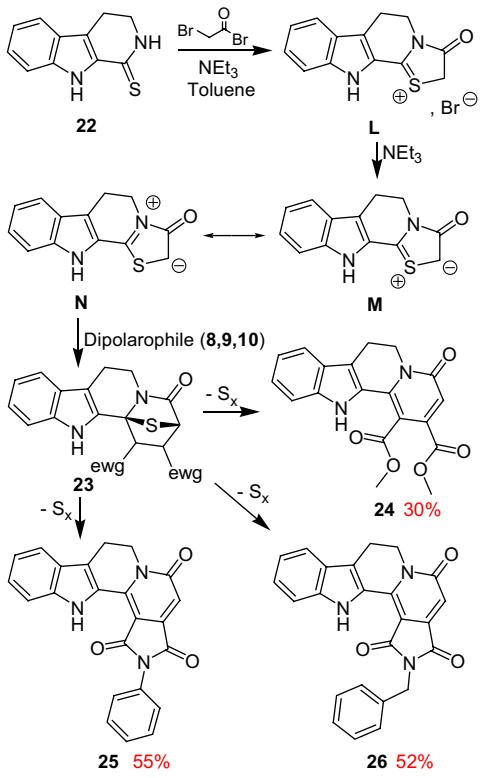
As highlight in Scheme 6, the formation of that product seems to proceed by a cascade process. This implies the formation of thionium ion **J**, its transformation with NEt_3 into corresponding thioisomünchnone salt **K** followed by the intramolecular 1,3-dipolar cycloaddition with **8** and desulfurization of the adduct in an ultimate step. This mechanistic paradigm was extended efficaciously to other dipolarophiles as **9** and **10**, but surprisingly the process stopped at the

bridgehead sulfur components **20** and **21**. Indeed, reaction of **18** with **9** and **10** furnished thiadiazacyclopenta[*c*]fluorenetriones **20** and **21** in 39% and 42% yields, respectively. From these results, the reaction appears tolerant with respect to the nature of dipolarophile and, importantly, it proceeds without any significant changes in the reaction yields.

The structure of these products was assigned on the basis on their IR, NMR (^{1}H and ^{13}C experiments including NOE difference and DEPT program, respectively) as well as elemental analyses. For instance, the ^{1}H NMR spectra of **19** showed a non-conventional doublet of doublet with J=17.12 Hz centered at δ=3.71 ppm, one singlet at δ=6.02 ppm characteristics of non-equivalent[23] methylene protons (CH_2–N) and a pyridone proton, respectively. On the other hand, the ^{1}H NMR spectra of fluorenetrione derivative **20** showed besides nine aromatic protons four aliphatic proton blocks. They consist of two doublets at δ=3.16 ppm and δ=3.42 ppm with coupling constant of about J=7.04 Hz (cis coupling between H_4 and H_5, see Scheme 6), a doublet of doublet for methylene protons (CH_2–N as an AB system, which appeared at δ=3.62 and 3.80 ppm with coupling constant J=16.43 Hz), and one singlet at δ=5.68 ppm attributed to H_3.[24] Interestingly, product **21** exhibits same profile with, in addition, an AB system at down field centered at δ=4.77 ppm with J=14.09 Hz. These data are consistent with the data described earlier by Potts et al.[2b,25] for the mesoionic *N*-phenylmaleimide adduct in the *endo* configuration. In these cases, the coupling constant between the 3 and 4 protons in the *endo* form was of about 1 up to 1.5 Hz indicating a trans coupling, and between the protons 4 and 5 it was of J=7 Hz consistent with a cis coupling. Our observations were in accordance with these values, indicating the formation of the thiadiazacyclopenta[*c*]fluorinetriones **20** and **21** in only the *endo* configuration.

For the generalization and additional demonstration of our tandem protocol, another class of thioisomünchnones fused to six-membered azacyclic system was investigated (Scheme 7). In the first step, the requisite 2,3,4,9-tetrahydro-β-carboline-1-thione (**22**) was prepared by two pathways from tryptamine. In fact, the reaction of tryptamine with phosgene in dry toluene gave 2,3,4,9-tetrahydro-β-carboline-1-one in 78% yield. The thioamide **22** was obtained in an ultimate step by thionation of the amide with Lawesson's reagent in toluene in 82% yield.[26] This product was also obtained directly in one step, with however very modest yield of 29%, when tryptamine was treated with the NEt_3/$ClCO_2Et$ combination in the presence of CS_2 used as reactant and solvent.

As showed in Scheme 7, the reaction of the above 2,3,4,9-tetrahydro-β-carboline-1-thione (**22**) with 2-bromoacetyl bromide (1.1 equiv) and triethylamine (1 equiv) in toluene gave the corresponding thionium cation **L**. By its heating with additional 1 equiv of triethylamine the mesoionic salt **M** was generated and this underwent an external 1,3-dipolar cycloaddition and desulfurization with methyl acetylenedicarboxylate (**8**) to give after chromatography purification methyl 4-oxo-4,6,7,12-tetrahydroindolo[2,3-*a*]quinolizine-1,2-dicarboxylate (**24**) as red-orange solid in 30% yield. Here, the tandem route evoked above was evidenced since the desulfurization of the key adduct intermediate **23**



Scheme 7. Tandem process giving *N*-substituted indoloquinolizinone products **24**, **25**, and **26**.

(ewg=CO_2Me) was effective without additional heating. In this case, all the tentative made for isolation of the intermediate **23** failed.

With *N*-phenylmaleimide (**9**) and *N*-benzylmaleimide (**10**) as dipolarophiles, the betaine **M**[27] under reflux in toluene gave an extremely colorless solution, which after a classical work up, indicated the presence of only one product identified as indolopyrroloquinolizinones **25** and **26** (Scheme 7). These results demonstrate the effectiveness of the betaine formation → intramolecular 1,3-dipolar cycloaddition → desulfurization tandem process and the products were isolated in appreciable yields of 55% and 52%, respectively, more better than the ones indicated for related structures as above. This could be explained by the fact that 1,3-thiazolium-4-olates salts in β-carboline series were more stable in thermal conditions than betaines formed above in pyrrolidinone, isoindolinone, and indolinone heterocycles.

Again, the structure of these products was secured by the NMR study. Thus, the ^{1}H NMR spectra of **24**, **25**, and **26** showed two triplets characteristics of –N–CH_2–CH_2– functionality from δ=3.11 to 3.19 ppm and from δ=4.47 to 4.89 ppm, respectively, with coupling constants of about J=7.03–7.04 Hz. Especially diagnosis was made by the presence of a singlet proton at δ=6.91, 7.02, and 6.92 ppm for structures **24**, **25**, and **26**, respectively, characteristic of the formation of the pyridone nucleus. These values were in accordance with those reported for compounds containing the pyridone ring bearing an hydrogen atom at the α-position of the thiolactam function.[8a,28] In the concomitant fashion, the ^{13}C NMR spectra of these products also showed two methine carbons, which inverted in the DEPT-135

experiments. In the case of product **26**, an additional methine carbon corresponding to the benzyl group also appeared at δ=6.92 ppm in the ^{13}C NMR spectra but inverted in the ^{13}C NMR, recorded using DEPT-135 technique. These values, as well as elemental analyses are in accordance with the proposed structures.

3. Conclusion

In summary, we have demonstrated the utility of 1,3-thiazolium-4-olates salts, derived from pyrrolidine-2-thione (**7**) and isoindoline-1-thione (**16**), to create with dipolarophiles a set of diverse and new thiapyrrolizidinones. The reaction seems to proceed with a hydrogen abstraction as well as addition of the dipolarophile. This consequently induces the interruption of the 1,3-dipolar cycloaddition process in the intramolecular fashion.

Further, with thioisomünchnones in benzene and indole series not possessing a hydrogen atom at β-position of the sulfur atom, the tandem betaine formation/intramolecular 1,3-dipolar cycloaddition/desulfurization process was effective and led to fused pyridones and quinolizinones products **19** and **24**–**26**. Elsewhere, in the case of 2,3-dihydroisoindole-1-thione (**18**) as a betaine precursor, thiadiazacyclopenta[*c*]fluorenetrione derivatives **20** and **21** exclusively in *endo* configuration were formed in an interruption of the tandem process as outlined above. Finally, the yields associated with obtaining these products were generally ranged from 30% to 65%. The latter were higher in betaines derived from β-carboline.

Finally, these processes might find applications as valuable strategies in syntheses of potentially active and bioactive compounds. Studies along this line are currently underway in our laboratory, and the results will be published soon.

4. Experimental

4.1. General

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra of solids (potassium bromide) and liquids (neat) were recorded on a Perkin–Elmer FTIR paragon 1000 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 (300 MHz) instrument in deuteriochloroform unless other indicated solvent and chemical shifts (δ) are expressed in parts per million relative to TMS as internal standard. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F_{254} (Merck) and the spots were visualized using an ultraviolet lamp or an iodine vapor. Mass spectral measurements were recorded on a AEI MS 902 S spectrophotometer. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mont-Saint-Aignan, France.

4.2. General procedure for the reaction of thioisomünchnones with dipolarophiles

To a solution of thioamide (4.94 mmol) in 30 mL of dry toluene was added 0.47 mL (5.39 mmol) of 2-bromoacetyl bromide at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 30 min and then heated at 100 °C for 3 h. After cooling, 1.39 mL (9.89 mmol) of triethylamine was added to the solution at room temperature followed 10 min after by dropwise addition of a solution of 7.39 mmol of the expected dipolarophile dissolved in 10 mL of dry toluene. The mixture was heated at reflux for an additional 12 h, cooled to room temperature, concentrated under reduced pressure, and chromatographed on a silica gel column using a cyclohexane/AcOEt (4/1) as eluting mixture to give solids in yields ranging from 30% to 65%.

4.2.1. Dimethyl (*Z*)-2-(3-oxo-(5,6-dihydropyrrolo[2,1-*b*]thiazol-2(3*H*)-ylidene)succinate (11). This product was isolated as a yellow solid in 49% yield and melted at 147–149 °C; IR (KBr) $\bar{\nu}_{max}$=2977 (CH), 1738 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (dt, 2H, *J*=7.82 and 5.48 Hz, CH_2–N), 3.71 (s, 2H, CH_2), 3.73 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.91 (dt, 2H, *J*=7.04 Hz, CH_2–CH=), 6.98 (t, 1H, *J*=5.48 Hz, CH=); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.6 (CH_2), 31.2 (CH_2), 48.2 (CH_2), 52.1 (CH_3), 52.3 (CH_3), 131.3 (C^q), 138.9 (CH=), 152.4 (C^q), 155.2 (C^q), 168.0 (C=O), 168.3 (C=O), 173.0 (C=O); Anal. Calcd for $C_{12}H_{13}NO_5S$ (283.31): C, 50.88%; H, 4.63%; N, 4.94%. Found: C, 50.65%; H, 4.44%; N, 4.81%.

4.2.2. 3-(3-Oxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-2-yl)-1-phenylpyrrolidine-2,5-dione (12). This product was isolated as an orange solid in 45% yield and melted at 152–154 °C; IR (KBr) $\bar{\nu}_{max}$=3000 (CH), 2985 (CH), 1717 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.19–2.51 (m, 2H, CH_2), 2.55–2.80 (m, 1H, CH), 3.12–3.27 (m, 1H, CH), 3.45–3.63 (m, 2H, 2CH), 3.75–3.78 (m, 1H, CH), 4.36 (d, 1H, *J*=2.35 Hz, CH–S), 7.21–7.24 (m, 3H, CH_{aro}+CH=), 7.25–7.46 (m, 3H, CH_{aro}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.6 (CH_2), 29.1 (CH_2), 42.7 (CH_2), 47.7 (CH), 55.4 (CH), 58.4 (CH), 86.1 (C^q), 126.5 (2×CH), 129.2 (CH), 129.4 (2×CH), 131.6 (C^q), 170.4 (C=O), 173.1 (C=O), 173.7 (C=O); Anal. Calcd for $C_{16}H_{12}N_2O_3S$ (314.07): C, 61.13%; H, 4.49%; N, 8.91%. Found: C, 61.00%; H, 4.31%; N, 8.69%.

4.2.3. 1-Benzyl-3-(3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-2-yl)-1-pyrrolidine-2,5-dione (13). This product was isolated as a yellow solid in 41% yield and melted at 158–160 °C; IR (KBr) $\bar{\nu}_{max}$=3011 (CH), 2982 (CH), 1709 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15–2.45 (m, 2H, CH_2), 2.55–2.72 (m, 1H, CH), 3.08–3.23 (m, 1H, CH), 3.31 (d, 1H, *J*=7.04 Hz, CH), 3.40–3.57 (m, 1H, CH), 3.67 (dd, 1H, *J*=6.34 and 1.57 Hz, CH), 4.23 (d, 1H, *J*=7.04 Hz, CH–S), 4.64 (d, 2H, *J*=2.35 Hz, CH_2–N), 7.25–7.35 (m, 6H, CH_{aro}+CH=); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.5 (CH_2), 28.9 (CH_2), 42.6 (CH_2), 43.1 (CH_2), 47.7 (CH), 55.5 (CH), 57.9 (CH), 85.6 (C^q), 128.1 (CH), 128.7 (2×CH), 129.0 (2×CH), 135.1 (C^q), 173.7 (C=O), 174.2 (C=O), 178.4 (C=O); Anal. Calcd for $C_{17}H_{14}N_2O_3S$ (328.09): C, 62.18%; H, 4.91%; N, 8.53%. Found: C, 62.01%; H, 4.76%; N, 8.42%.

4.2.4. Thiazolo[3,2-*a*]indol-3-one (17). This product was isolated as a yellow solid in 65% yield and melted at 136–138 °C (lit.[20] 141–143 °C); IR (KBr) $\bar{\nu}_{max}$=3009 (CH),

2965 (CH), 1718 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.20 (s, 2H, CH_2), 6.85 (s, 1H, CH), 7.15–7.31 (m, 2H, CH_{aro}), 7.36–7.44 (m, 1H, CH_{aro}), 8.09 (dd, 1H, J=6.26 and 3.91 Hz, CH_{aro}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.4 (CH_2), 100.4 (CH), 113.0 (CH), 119.6 (CH), 122.9 (CH), 122.9 (CH), 124.8 (CH), 132.0 (C^q), 135.7 (C^q), 136.8 (C^q), 166.6 (C=O); Anal. Calcd for $C_{10}H_7NOS$ (189.02): C, 63.47%; H, 3.73%; N, 7.40%. Found: C, 63.21%; H, 3.65%; N, 7.12%.

4.2.5. Methyl 4-oxo-4,6-dihydropyrido[2,1-*a*]isoindole-1,2-dicarboxylate (19). This product was isolated as a brown solid in 40% yield and melted at 104–106 °C; IR (KBr) $\bar{\nu}_{max}$=3004 (CH), 2942 (CH), 1767 (C=O), 1732 (C=O), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.71 (dd, 2H, J=17.12 Hz, CH_2), 3.79 (s, 3H, CH_3), 5.57 (s, 3H, CH_3), 6.02 (s, 1H, CH), 7.03–7.19 (m, 2H, $2CH_{aro}$), 7.39 (d, 1H, J=7.05 Hz, CH_{aro}), 7.50 (d, 1H, J=6.26 Hz, CH_{aro}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.1 (CH_2), 52.9 (CH_3), 53.0 (CH_3), 113.0 (CH), 121.3 (CH), 122.1 (CH), 126.6 (CH), 126.9 (CH), 146.2 (C^q), 146.9 (C^q), 150.6 (C^q), 153.1 (C^q), 154.5 (C^q), 161.6 (C=O), 162.1 (C=O), 163.6 (C=O); Anal. Calcd for $C_{16}H_{13}NO_5$ (299.08): C, 64.21%; H, 4.38%; N, 4.68%. Found: C, 64.04%; H, 4.15%; N, 4.43%.

4.2.6. 3*a*,7,11*b*,11*c*-Tetrahydro-2-phenyl-4,11*b*-thia-2,6-diazacyclopenta[*c*]fluorene-1,3,5(4*H*)-trione (20). This product was isolated as a brown solid in 39% yield and melted at 218–220 °C; IR (KBr) $\bar{\nu}_{max}$=3019 (CH), 2936 (CH), 1718 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.16 (d, 1H, J=7.04 Hz, CH), 3.42 (d, 1H, J=7.04 Hz, CH), 3.62 (d, 1H, J=16.43 Hz, CH_2–N), 3.80 (d, 1H, J=16.43 Hz, CH_2–N), 5.68 (s, 1H, CH), 7.22–7.36 (m, 4H, H_{aro}), 7.38–7.55 (m, 5H, H_{aro}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.5 (CH_2), 51.3 (CH), 55.0 (CH), 59.9 (CH), 80.4 (C^q), 120.4 (CH), 121.1 (CH), 125.6 (2CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 129.4 (2×CH), 131.4 (CH), 143.6 (C^q), 145.5 (C^q), 168.1 (C=O), 171.4 (C=O), 173.4 (C=O); Anal. Calcd for $C_{20}H_{14}N_2O_3S$ (362.07): C, 66.28%; H, 3.89%; N, 7.73%. Found: C, 66.02%; H, 3.64%; N, 7.55%.

4.2.7. 2-Benzyl-3*a*,7,11*b*,11*c*-tetrahydro-4,11*b*-thia-2,6-diazacyclopenta[*c*]fluorene-1,3,5(4*H*)-trione (21). This product was isolated as a brown solid in 42% yield and melted at 208–210 °C; IR (KBr) $\bar{\nu}_{max}$=3003 (CH), 2976 (CH), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.98 (d, 1H, J=7.04 Hz, CH), 3.26 (d, 1H, J=7.04 Hz, CH), 3.46 (s, 2H, CH_2–N), 4.66 (d, 1H, J=14.09 Hz, CH_2–N), 4.77 (d, 1H, J=14.09 Hz, CH_2–N), 5.57 (s, 1H, CH), 7.15–7.44 (m, 9H, H_{aro}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.3 (CH_2), 43.3 (CH_2), 51.3 (CH), 55.0 (CH), 59.4 (CH), 80.4 (C^q), 120.2 (CH), 120.9 (CH), 128.2 (CH), 128.3 (CH), 128.7 (CH), 128.9 (2×CH), 130.4 (2×CH), 135.4 (C^q), 143.5 (C^q), 145.9 (C^q), 167.1 (C=O), 171.9 (C=O), 173.9 (C=O); Anal. Calcd for $C_{21}H_{16}N_2O_3S$ (376.09): C, 67.00%; H, 4.28%; N, 7.44%. Found: C, 66.87%; H, 4.03%; N, 7.21%.

4.2.8. Methyl 4-oxo-4,6,7,12-tetrahydroindolo[2,3-*a*]-quinolizine-1,2-dicarboxylate (24). This product was isolated as a red-orange solids in 30% yield and melted at 164–166 °C; IR (KBr) $\bar{\nu}_{max}$=3006 (CH), 2965 (CH), 1784 (C=O), 1760 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.11 (t, 2H, J=7.04 Hz, CH_2), 3.86 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.47 (t, 2H, J=7.04 Hz, CH_2), 6.91 (s, 1H, CH), 7.17 (t, 1H, J=7.04 Hz, CH_{aro}), 7.29 (t, 1H, J=7.05 Hz, CH_{aro}), 7.43 (d, 1H, J=7.82 Hz, CH_{aro}), 7.61 (d, 1H, J=7.83 Hz, CH_{aro}), 9.94 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3 (CH_2), 41.5 (CH_2), 53.2 (CH_3), 53.5 (CH_3), 106.0 (C^q), 112.3 (CH), 118.8 (C^q), 119.1 (CH), 119.7 (CH), 120.9 (CH), 124.5 (C^q), 125.8 (CH), 128.5 (C^q), 137.8 (C^q), 138.9 (C^q), 140.9 (C^q), 161.5 (C=O), 165.9 (C=O), 169.7 (C=O); Anal. Calcd for $C_{19}H_{16}N_2O_5$ (352.11): C, 64.77%; H, 4.58%; N, 7.95%. Found: C, 64.45%; H, 4.33%; N, 7.76%.

4.2.9. 7,8-Dihydro-2-phenylindolo[2,3-*a*]pyrrolo[3,4-*a*]quinolizine-1,3,5(13*H*)-trione (25). This product was isolated as a red-orange solid in 55% yield and melted at 234–236 °C; IR (KBr) $\bar{\nu}_{max}$=3010 (CH), 2954 (CH), 1756 (C=O), 1742 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.24 (t, 2H, J=7.03 Hz, CH_2), 4.59 (t, 2H, J=7.03 Hz, CH_2), 7.02 (s, 1H, CH), 7.12–7.30 (m, 2H, CH_{aro}), 7.32–7.69 (m, 7H, CH_{aro}), 12.04 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 18.7 (CH_2), 20.8 (CH_2), 111.4 (CH), 113.2 (CH), 119.0 (C^q), 119.4 (CH), 120.6 (CH), 123.9 (C^q), 124.3 (C^q), 124.7 (CH), 126.2 (C^q), 127.6 (2×CH), 128.6 (CH), 128.9 (2×CH), 131.5 (C^q), 138.0 (C^q), 139.8 (C^q), 140.3 (C^q), 161.8 (C=O), 164.6 (C=O), 167.0 (C=O); Anal. Calcd for $C_{23}H_{15}N_3O_3$ (381.39): C, 72.43%; H, 3.96%; N, 11.02%. Found: C, 72.21%; H, 3.77%; N, 10.86%.

4.2.10. 2-Benzyl-7,8-dihydroindolo[2,3-*a*]pyrrolo[3,4-*a*]quinolizine-1,3,5(13*H*)-trione (26). This product was isolated as a red-orange solid in 52% yield and melted at 230–232 °C; IR (KBr) $\bar{\nu}_{max}$=3017 (CH), 2948 (CH), 1757 (C=O), 1749 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.19 (t, 2H, J=7.04 Hz, CH_2), 4.52 (t, 2H, J=7.04 Hz, CH_2), 4.89 (s, 2H, CH_2–N), 6.92 (s, 1H, CH), 7.14–7.59 (m, 9H, CH), 12.10 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0 (CH_2), 41.4 (CH_2), 41.8 (CH_2), 112.3 (CH), 118.7 (C^q), 119.6 (CH), 120.4 (CH), 123.6 (C^q), 123.8 (C^q), 123.9 (C^q), 124.5 (C^q), 126.2 (CH), 127.6 (CH), 128.1 (2×CH), 128.3 (2×CH), 128.5 (CH), 135.1 (C^q), 138.1 (C^q), 139.7 (C^q), 162.0 (C=O), 164.8 (C=O), 167.3 (C=O); Anal. Calcd for $C_{24}H_{17}N_3O_3$ (395.13): C, 72.90%; H, 4.33%; N, 10.63%. Found: C, 72.78%; H, 4.14%; N, 10.46%.

Acknowledgements

The authors are grateful to the Libyan Government for a Graduate Fellowship (2002–2005) attributed to A.H. We are also grateful for many fruitful discussions throughout the course of this work with Prof. B. Decroix.

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