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Aza-Annulation as a Versatile Approach to the Synthesis of Non-Benzodiazepene Compounds for the Treatment of Sleep Disorders

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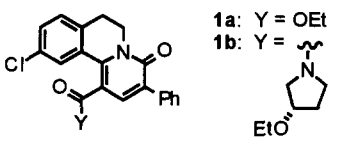
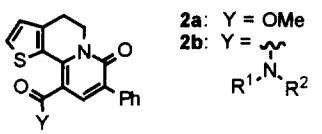
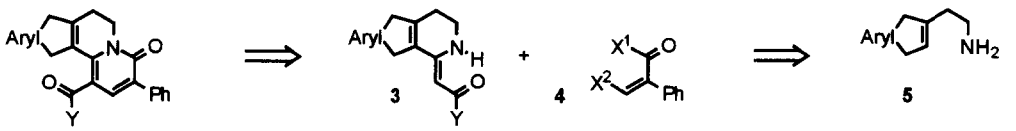
Abstract: The aza-annulation of enamino ester substrates has been demonstrated as an efficient alternative to the syntheses of non-benzodiazepine sleep inducers. Enamino ester substrates derived from aryl, thiophene, and indole functionality were prepared from the corresponding ethyl amines by isothiocyanate formation followed by acid catalyzed cyclization.

Investigators at Hoffmann La-Roche, Ltd have reported structural alternatives to molecules with benzodiazepine scaffolds for the treatment of anxiety and sleep disorders.[1] These non-benzodiazepine heterocycles include the structural types illustrated by **1** and **2**, which have shown promise as effective non-sedative hypnotic compounds for the induction and maintenance of sleep for individuals with sleep disorders.

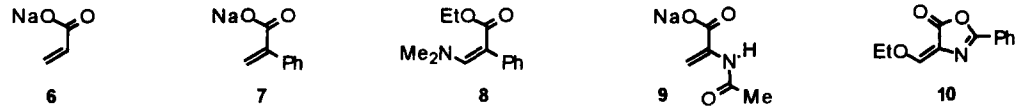




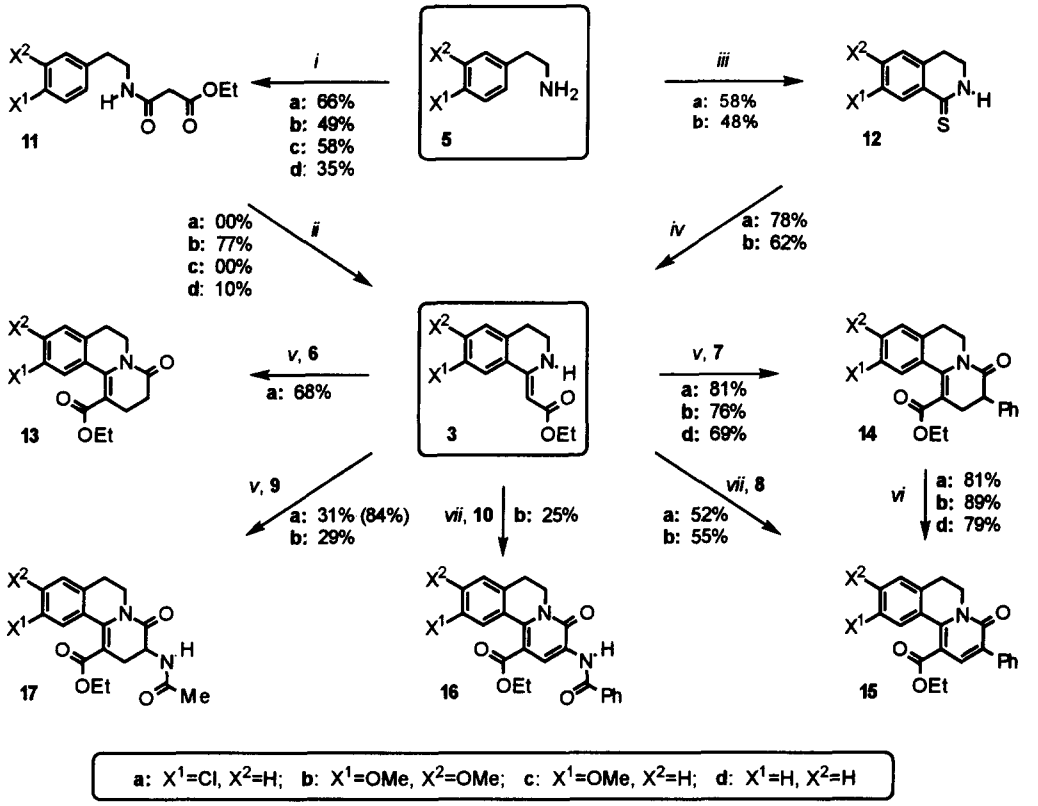
Our interest in these molecules stemmed from the presence of the pyridone substructural feature, which has been prepared through aza-annulation of enamino amides and esters (**3**) with acrylate derivatives (**4**).[2] Aza-annulation methodology with activated acrylate derivatives has been effective for construction of pyridone[3] and dihydropyridone compounds in the synthesis of natural products[4] and molecules with peptide features.[5]



A number of acrylate reagents (**6-10**) have been studied for the aza-annulation of enamine substrates. For example, reagents **6**, **7**, and **9** can be activated by treatment with EtO_2CCl to give dihydropyridone aza-annulation products, while **8** and **10** react with enamine substrates at elevated temperatures to provide pyridone products.[4,5] Although products such as **1** and **2** can be prepared with an α-Ph group (from **7** and **8**[6]), interesting analogs that contain α-amido functionality (from **9** and **10**) can also be constructed.[3a]



Scheme 1. Synthesis and Elaboration of Enamino Ester **3**.[a]



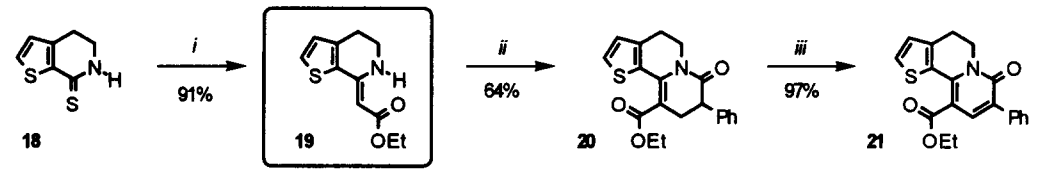
[a]Reaction conditions:[7] (*i*) $ClCOCH_2CO_2Et$ ($KO_2CCH_2CO_2Et/(ClCO)_2$), K_2CO_3, Et_2O or CH_2Cl_2; (*ii*) $POCl_3$, MeCN, reflux. (*iii*) (a) CS_2, Et_3N, $ClCO_2Et$,[8] (b) $AlCl_3$ or PPA;[8] (*iv*) $BrCH_2CO_2Et$, Et_3N, PPh_3, MeCN;[9] (*v*) **6**, **7**, or **9**, $ClCO_2Et$, THF, RT;[12] (*vi*) DDQ, toluene, reflux; (*vii*) **8** or **10**, DMF, reflux.

The initial challenge in the synthesis of **1** was the conversion of **5** to **3**, which did not work well under typical Bischler-Napieralski conditions (through **11**), and has led to the need for alternative methods (Scheme 1).[1] For this cyclization to succeed, an electron rich aromatic ring was necessary (**11b**). An alternative route, formation of thiolactam **12**, through a two-step isothiocyanate formation and acid catalyzed closure,[8] followed by Eschenmoser sulfide contraction, provided an efficient general route to the desired enamino ester **3**.[9]

The efficiency of enamino ester aza-annulation was dependent on the nature of the acrylate reagent used (Scheme 1). Treatment with **6** under standard aza-annulation conditions led to the formation of **13**,[10] and reaction with **7** provided slightly higher yields of **14**.[11] Formation of sleep inducer **1a** was performed either by the two step aza-annulation/DDQ oxidation conversion of **14a** to **15a** (66% yield from **3**) or by direct aza-annulation of **3a** with **8**, which was not quite as efficient (52%). Similar results were obtained when the electron rich (**3b**) and unsubstituted (**3d**) substrates were studied. Conversion of the ester functionality in this class of molecules (**1a**) into their corresponding amides (**1b**) has already been established.[1] Interestingly,

reagents **9** and **10** were less reactive than **6-8**. In addition, the α-amino acid derivatives **16** and **17** were not formed as effectively as analogous products from aliphatic enamino esters, which led to incomplete conversion (31%; **3a** to **17a**; 84% based on recovered **3a**).[3]

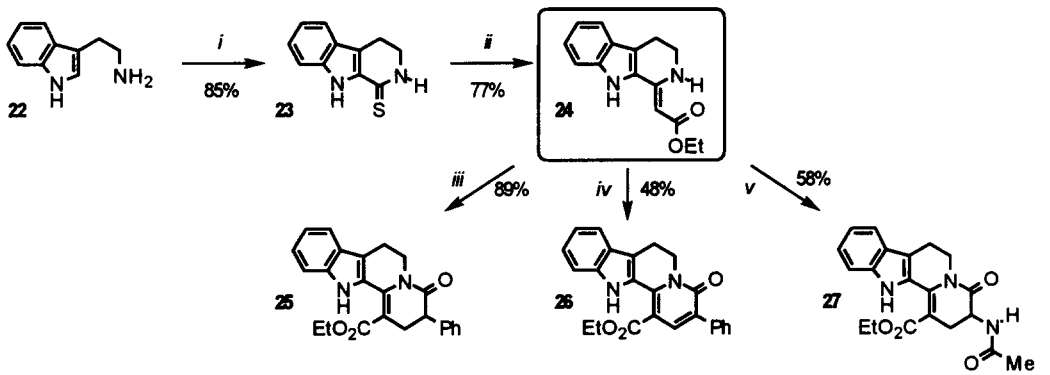
Scheme 2. Synthesis and Elaboration of Enamino Ester **19**.[a]



[a]Reaction conditions:[7] (*i*) $BrCH_2CO_2Et$, Et_3N, PPh_3, MeCN;[9] (*ii*) 7, $ClCO_2Et$, THF, RT;[10] (*iii*) DDQ, toluene, reflux.

The ethyl ester derivative (**21**) of the second sleep inducer, **2a**, was also prepared through the aza-annulation approach (Scheme 2). From previously reported **18**,[1b] Eschenmoser sulfide contraction proceeded smoothly to give **19**. Aza-annulation with **7**, activated with EtO_2CCl, gave **20** in moderate yield, and subsequent oxidation with DDQ efficiently generated **21**.

Scheme 3. Synthesis and Elaboration of Enamino Ester **24**.[a]



[a]Reaction conditions:[7] (*i*) (a) CS_2, Et_3N, $ClCO_2Et$,[8] (b) PPA;[8] (*ii*) $BrCH_2CO_2Et$, Et_3N, PPh_3, MeCN;[9] (*iii*) 7, $ClCO_2Et$, THF, reflux; (*iv*) **8**, glacial AcOH, 95 °C, 2 h; (*v*) **9**, $ClCO_2Et$, THF, RT.

Our fascination with this structural class of molecules led to the extension of this aza-annulation methodology to the corresponding tryptamine (**22**) analogs of the sleep inducers (Scheme 3).[12] Formation of the intermediate isothiocyanate, followed by acid catalyzed intramolecular cyclization, proceeded in good yield to give thiolactam **23**. Subsequent conversion to the enamino ester **24** was accomplished in 77% yield. From **24**, aza-annulation was achieved in 89% yield to give **25**, and the unsaturated analog **26** was formed directly by treatment of **24** with **8**. The corresponding α-amido derivative **27** was generated by reaction with the corresponding acrylate derivative **9**.

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9. Typical procedure for the synthesis of **3**: To a solution of thiolactam (1.0 equiv.)[8] was added $BrCH_2CO_2Et$ (1.2 equiv.), and the mixture was stirred for 24-36 h. The solvent was removed, the thionium salt was dissolved in MeCN (0.3 *M*), Et_3N (1.5 equiv.) was added, and the mixture was stirred at RT for 15 min. After this time, Ph_3P (1.2 equiv.) was added, the mixture was stirred for 15 min, Et_3N (1.5 equiv.) was added, and the solution was heated at reflux for 40-70 h. The dark brown mixture was concentrated, and the product was purified by flash column chromatography.[7]
10. Typical procedure for the aza-annulation reaction of **3**: A solution of the activated acrylate derivative (freshly prepared by the addition of the corresponding acrylic acid to NaH in THF at -78 °C followed by the addition of EtO_2CCl) was added to a solution of the enamine in THF at RT, and the mixture was stirred for 12-18 h. Reactions were quenched by the addition of H_2O, the mixture was extracted with either Et_2O or EtOAc (4 x 20 mL), the combined organic fractions dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography.[7]
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