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Intermolecular Transfer of an Alkenyl Group in Enamines: Application to Synthesis of [*b*]-Fused Pyridines

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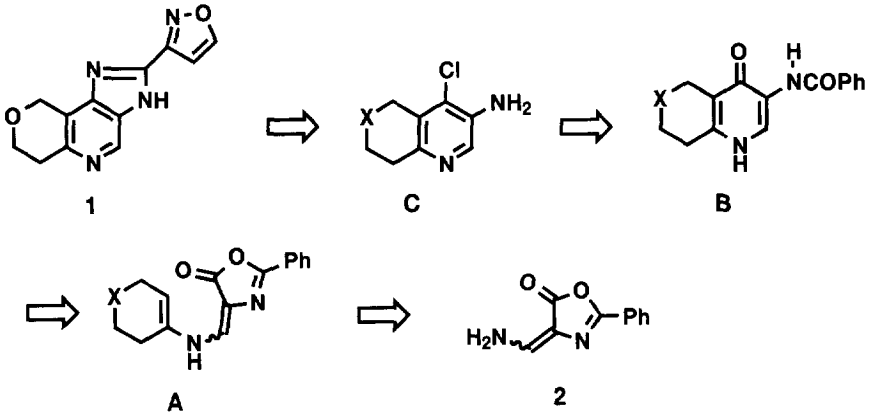
Abstract: A novel intermolecular alkenyl transfer of enamines was developed for the preparation of cycloalkenylaminomethyleneoxazolones, which were thermally cyclized to [*b*]-fused pyridines in good yields. The functional manipulation of the pyridines provided versatile precursors for further annulation to tricyclic ring systems.Copyright © 1996 Elsevier Science Ltd

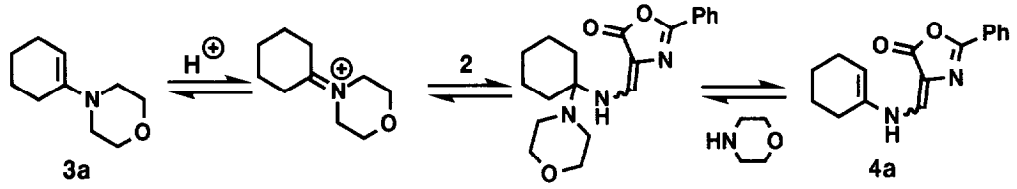
Recently, we reported the synthesis and structure activity relationships of a new series of benzodiazepine receptor ligands, from which **S-8510**, a monophosphate salt of 2-(3-isoxazolyl)-3,6,7,9-tetrahydroimidazo-[4,5-*d*]pyrano[4,3-*b*]pyridine (**1**) was selected as a clinical candidate for the treatment of senile dementia.[1] During the study for large-scale production [2] of **1**, we have found a novel intermolecular transfer of an alkenyl group of morpholine enamines to a low basic amino group. In this communication, we describe a preparation of cycloalkenylaminomethyleneoxazolones by use of the alkenyl transfer and their conversions to versatile [*b*]-fused pyridines.

We envisioned that fused pyridine **C** would be a suitable precursor of **1** and its analogs. Compound **C** could be prepared from **B**, which would be obtainable through cyclization of **A**. Compound **A** would be derived from readily available aminomethyleneoxazolone **2** [3] and a cyclic ketone.



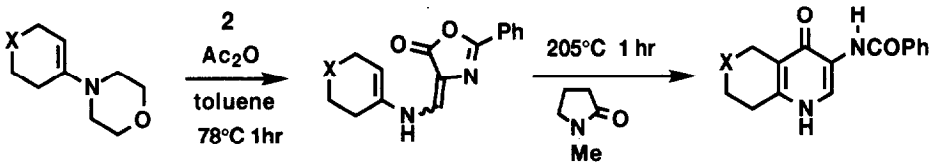
To test this idea, condensation of **2** with cyclohexanone in the presence of a catalyst was examined in

order to produce compound **A** (X = CH_2). All attempts failed, presumably due to the low basicity of the amino group of **2**. However, we fortunately found that **4a** formed as a crystalline precipitate (ca. 30% yield) when **2** was heated at 60°C with 1-morpholino-1-cyclohexene (**3a**) in acetic acid for 20 min. The yield was improved using acetic anhydride as a solvent (55°C, 1 hr, 72% yield). This reaction could be explained by the intermolecular transfer of the cyclohexenyl group on the morpholine nitrogen to the amino group of **2** following the equilibrium illustrated below. In this equilibrium, acetylation of the liberated morpholine with acetic anhydride was considered to facilitate the formation of **4a**. To our knowledge, this is the first example in which



an alkenyl group of an enamine transfers intermolecularly to an amino group of low basicity. Thermal cyclization of **4a** (205°C in 1-methyl-2-pyrrolidinone) produced **5a** (86% yield) as planned (Scheme 1). In order to extend this methodology to the synthesis of **1**, the reaction with **3b** was examined in detail. When a mixture of **2** and **3b** (1.2 equiv) in acetic anhydride was heated at 55°C for 1 hr, **4b** was obtained as a crystalline precipitate in 42% yield. Since the yield was assumed to mainly depend on the solubility of the product, the use of toluene as a cosolvent was attempted to provide higher yield according to the following procedure. A suspension of **2** (3.76 g, 0.02 mole) , **3b** (1.2 equiv) and acetic acetic anhydride (5 equiv) in toluene (37.6 mL) was heated up to 78°C. During this period of time, the reaction mixture became clear and then an yellow precipitate formed. After 1 hour, the mixture was cooled to ice-bath temperature and the resulting precipitate was filtered and washed with *i*-Pr_2O to afford **4b** as an orange solid in 83% yield.

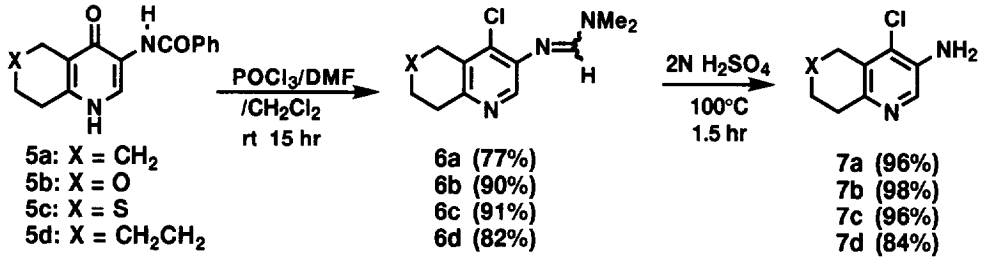
The resultant **4b** was shown to be a 4:1 mixture of geometrical isomers by means of H^1 NMR spectroscopy and HPLC analysis. The X-ray crystallographic analysis of the major isomer separated by recrystallization (*i*-PrOH—*i*-Pr_2O) established that syn-**4b** was predominantly formed.[4] When the 4:1 mixture of **4b** was heated in 1-methyl-2-pyrrolidinone at 200°C for 1 hr, the cyclized product **5b** was obtained in 79% yield. This finding, coupled with the suitability of anti-**4b** in cyclization, suggested that the syn to anti isomerizationt occurred during the thermal reaction.



Scheme 1

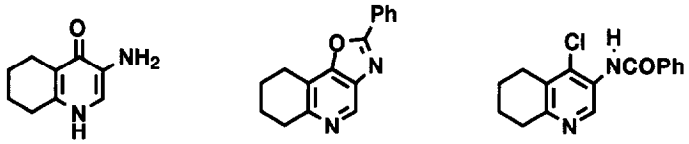
To explore the scope and limitations of the alkenyl transfer of enamines, the reaction with the enamines derived from other cyclic ketones was briefly examined. Morpholine enamines **3c** and **3d** were treated with **2** in

the above conditions to provide **4c** and **4d** in 75 and 64% yields, respectively. Cyclization of **4c** and **4d** proceeded to generate fused pyridines **5c** (92% yield) and **5d** (75% yield) as expected. In contrast to these results with the enamines derived from 6- and 7-membered cyclic ketones, the reaction of **2** with enamine **3e** (X = bond) derived from cyclopentanone resulted in the recovery of **2** without any products corresponding to **4**. It is interesting to note that neither **4e** nor **4a** was obtained using enamines prepared from other secondary amines (piperidine, pyrrolidine and ethyl-*n*-butylamine).



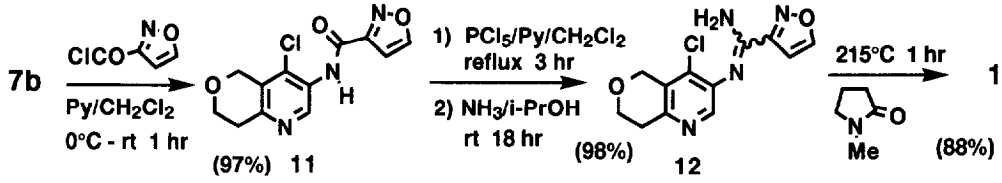
Scheme 2

Our next target was intermediate **C** which has appropriate functional groups for annulation of an additional heterocycle. Acid hydrolysis of **5a** (refluxed in conc. HCl) gave **8** in quantitative yield, but attempts at chlorination of **8** with $POCl_3$ or PCl_5 failed to produce **7a**. On the other hand, heating **5a** in $POCl_3$ afforded undesired oxazolopyridine **9** as a major product along with a minor amount of **10**. However, when **5a** was treated with $POCl_3$ in DMF and CH_2Cl_2 at room temperature, unexpected displacement [5] of the benzoyl group occurred to produce **6a** as a single clean product in good yield.[6] **6a** was readily converted to the desired **7a** by acid hydrolysis in 96% yield (Scheme 2). The same reactions with compounds **5b-d** proceeded smoothly to give **7b-d** in good overall yields.



8 **9** **10**

The resulting compounds **7** are useful intermediates as a precursor of tricyclic ring systems because the chloro substituent at the 4-position is reactive enough to be substituted by hetero atoms. All products in the sequence from **2** to **7** were isolated as practically pure solids by direct crystallization from the crude reaction mixture or by conventional workup without chromatographic purification. Therefore, this methodology is useful for large-scale production. Finally, transformation of **7b** to **1** proceeded in a straightforward manner as shown in Scheme 3.

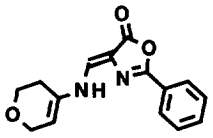


Scheme 3

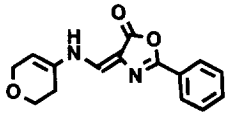
In conclusion, we found that the alkenyl group of a morpholine enamine transferred to the amino group of aminomethleneoxazolone **2** providing cycloalkenyl derivatives, which were readily converted to versatile [*b*]-fused 3-amino-4-chloropyridines in three steps. The transformation of **2** to **1** demonstrated that the route is potentially applicable to the synthesis of a variety of pharmaceutically important heterocyclic compounds.

REFERENCES AND NOTES

1. Takada, S.; Sasatani, T.; Chomei, N.; Adachi, M.; Fujishita, T.; Eigyo, M.; Murata, S.; Kawasaki, K.; Matsushita, A. *J. Med. Chem.*, **1996**, *39*, 2844-2851.
2. The synthetic method described in reference 1 was not applicable to large-scale (>1 kg) production of **1**, because utilization of hazardous nitration is required for the preparation of the starting material.
3. Preparation of **2** was accomplished in one pot in 60% yield by heating hippuric acid in ethyl orthformate and acetic anhydride, followed by evaporation and treatment with ammonia in *i*-PrOH. For the stepwise preparation via 4-(ethoxymethylene)-2-phenyl-5(4*H*)-oxazolone, see: Cornforth, J. W. Oxazoles and oxazolones. In *The Chemistry of Penicillin*, Clarke, H. T.; Johnson, J. R.; Robinson, R. Eds., Princeton University Press, 1949. pp. 688-848 (C.A., **1955**, 49, 3138-3151).
4. The structure of syn-**4b** determined by X-ray analysis and a possible structure of anti-**4b** are depicted below.



syn-4b



anti-4b

5. Alonso and co-workers have reported analogous reactions in which *N,N*-dimethylformamidine derivatives were unexpectedly produced in the Vilsmeier-Haack reaction of 2-phenylacetanilides bearing electron-releasing substiuents on the aromatic ring of anilides. See: Alonso, M. Á.; Úbeda, J. I.; Avendaño, C.; Menéndez, J. C.; Villacampa, M. *Tetrahedron*, **1993**, *49*, 10997-11008.
6. This was obtained as a single isomer. Its geometry has not been determined.

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