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A Novel Photo-assisted Annulation Reaction for the Synthesis of 6,7-Dichloroimidazo[4,5-b]quinolin-2-one

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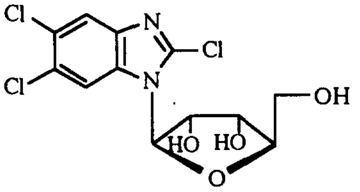
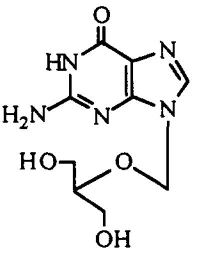
Key Words : Photo-assisted annulation, imidazo[4,5-b]quinolin-2-one

Abstract: A novel photo-assisted annulation was developed for the synthesis of 6,7-dichloroimidazo[4,5-b]quinolin-2-one. This mild ring closure method has circumvented problems associated with the previous methods and should tolerate a variety of functional groups.

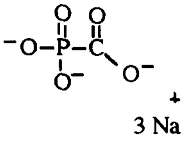
Recently, a series of polyhalogenated benzimidazole ribonucleosides have been synthesized and found[1] to be potent antiviral agents against human cytomegalovirus (HCMV) infections. The lead compound, 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) is more effective and less toxic than the current clinical agents, ganciclovir and foscarnet, against HCMV in cell culture studies. To study some key sub-structures of TCRB in a dimensionally stretched-out manner and the spatial limitation of targeted enzymes, a series of imidazo[4,5-b]quinoline ribonucleosides were designed as dimensional probes[2] of TCRB. In the proposed synthesis of these imidazo[4,5-b]quinoline ribonucleosides, 6,7-dichloroimidazo[4,5-b]quinolin-2-one (**8**) was required as a key heterocyclic intermediate.



TCRB



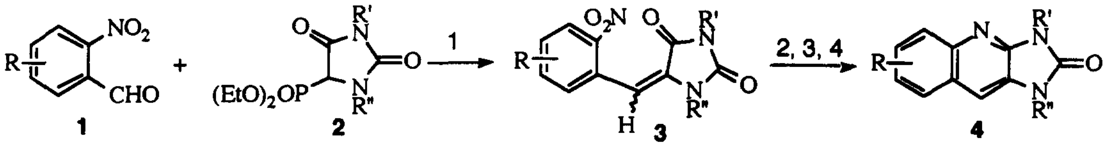
Ganciclovir



Foscarnet

A literature search revealed that the number of imidazo[4,5-b]quinolin-2-ones (**4**) being synthesized increased dramatically in the past few years due to the discovery that derivatives of **4** are potent inhibitors of blood platelet low Km cAMP phosphodiesterase and induced aggregation and exhibit antithrombotic activity in animal models.[3a] Thus, the development of convergent and efficient methods for the synthesis of **4** has become increasingly important. Except for one example,[4a] approaches for the synthesis of this parent structure have all involved a closure of the central ring as the final synthetic transformation either from 5-[(2-nitrophenyl)methyl]imidazolidin-2,4-diones[4b,3a] or from 5-[(2-nitrophenyl)methylene]imidazolidin-2,4-diones[4c,3a] (**3**). In an improved method recently reported by Meanwell and co-workers,[3] a Horner-Wadsworth-

Emmons' type of olefin-forming reaction was used for the condensation between diethyl 2,4-dioxoimidazolidine-5-phosphonates (**2**) and 2-nitrobenzaldehydes (**1**). By this method, **3** can be generated rapidly and reliably in excellent yields under mild conditions.



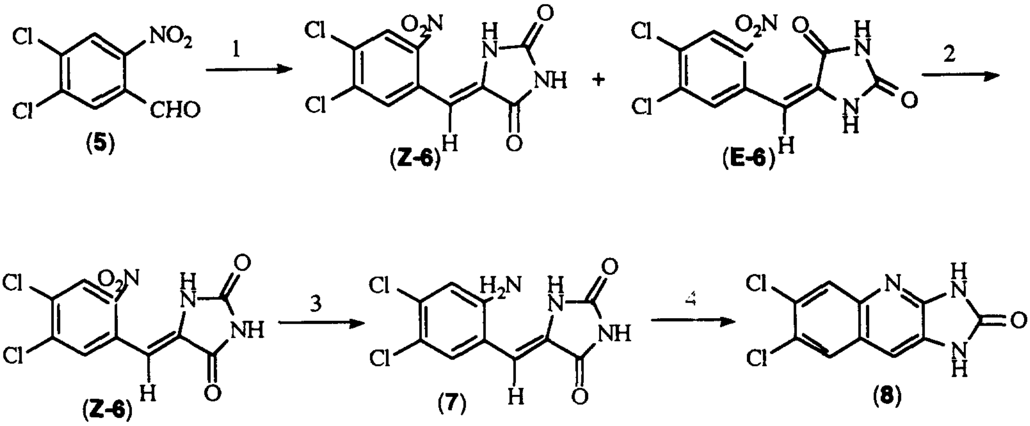
Reagents: 1. base. 2. 10% Pd/C, H_2 DMF. 3. TsOH, MeOH, Δ. 4. I_2, MeOH, Δ

However, to convert **3** to **4** by a closure of the central ring, both the nitro group and the double bond are reduced by a palladium catalyzed hydrogenation since the condensation reactions generate the Z-isomer of **3** as the major product. This limits the applications of this method since certain functional groups are not stable under these hydrogenation reduction conditions.

We elected to initially use an approach involving the Horner-Wadsworth-Emmons type of condensation to synthesize **8**, eventhough it was anticipated that the chloro substituents could cause some problems during the hydrogenation. A condensation between 4,5-dichloro-2-nitrobenzaldehyde[5] (**5**) and diethyl 2,4-dioxoimidazolidine-5-phosphonate[3b] with triethylamine in acetonitrile gave 5-[(4,5-dichloro-2-nitrophenyl)methylene]imidazolidin-2,4-dione (**6**) as a mixture of Z/E isomers (3/1) in a quantitative yield.[6] When **6** was subjected to hydrogenation conditions catalyzed by 10% Pd/C in DMF followed by an acid catalyzed ring closure and an oxidative aromatization, **8** was obtained in only a very low yield. A ^{1}H-NMR spectrum of the crude products revealed that severe dechlorination had occurred. Different catalysts, such as Raney Ni, 5% Pd/C and chloro tris(triphenylphosphine)rhodium, were tried without success. This confirmed our initial reservations regarding the applicability of this approach towards the synthesis of the target compounds. We would now like to report a novel photo-assisted annulation reaction which provides the desired compounds and should tolerate or accomodate a variety of functional groups.

The major purpose for a reduction of the double bond is to facilitate a rotation of the 2,4-dioxoimidazolidine moiety of **Z-6** in order to accomplish the subsequent ring closure. An alternative method of accomplishing this rotation without reducing the double bond would be to effect a double bond photo isomerization. Double bond photo isomerizations are well documented in the literature.[7] The ratio of Z/E isomers at a photo stationary state depends on many factors such as irradiation wavelength, photo sensitizers and solvents. We surmised that if the amino derivative of **6** could ring close to give **8** during the double bond photo isomerization, it would provide an additional driving force to push the photo equilibrium in the direction of the E-isomer. When the mixture of Z/E isomers of **6** was subjected to iron reduction conditions, compound **8** was isolated along with Z-5-[(2-amino-4,5-dichlorophenyl)methylene]imidazolidin-2,4-dione[8] (**7**). Apparently, **E-6** underwent a ring closure under these reaction conditions once the nitro group was reduced. However, the rather insoluble solid (**8**) was very difficult to isolate from the solid mixture of Fe and FeO_n. To circumvent this problem, the mixture of Z/E isomers of **6** was first treated with sodium hydroxide to completely convert **E-6** to

Z-6.[3b] The nitro group of **Z-6** was then selectively reduced by an iron reduction reaction to give **7** in a quantitative yield. As we expected, when **7** in acetic acid was irradiated by a medium pressure mercury lamp at room temperature, 40 % of **8** was isolated. Some side-products were also generated under these conditions as detected by TLC. However, when a cupric sulfate/ammonium hydroxide filter solution[7b] was placed outside the mercury lamp to filter out wavelengths shorter than 405 nm, **8** was generated in a 90 % yield after 36 hours irradiation in acetic acid at room temperature.[9] Apparently, by using such a soft UV source, the amount of side-products were greatly reduced.



Reagents: 1. diethyl 2,4-dioxoimidazolidine-5-phosphonate, Et_3N, CH_3CN. 2. a). NaOH. b). HCl.
3. Fe, $FeSO_4$, MeOH, H_2O. 4. hγ, AcOH, r.t.

In conclusion, a novel photo-assisted annulation reaction was developed for the synthesis of imidazo[4,5-b]quinolin-2-ones which avoids a reduction of the double bond by stringent hydrogenation conditions and should tolerate a variety of functional groups. By this method, 6,7-dichloroimidazo[4,5-b]quinolin-2-one (**8**) was synthesized from **6** in an overall 90 % yield. The scope and limitations of this reaction for the synthesis of additional imidazo[4,5-b]quinolin-2-ones are now under investigation.

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6. Pure **Z-6** (63 %) and **E-6** (14 %) were isolated by crystallization from the mixture of Z/E isomers. **Z-6**: ^{1}H-NMR (DMSO-d_6): δ 11.3 (bs, 2H, =NH), 8.41 (s, 1H, aromatic H), 7.94 (s, 1H, aromatic H), 6.51 (s, 1H, olefinic H); ^{13}C NMR (DMSO-d_6): δ 164.20, 154.96, 146.14, 136.45, 132.14, 132.03, 130.64, 128.06, 126.10, 99.62; *Anal.* Calcd for $C_{10}H_5Cl_2N_3O_4$(302): C, 39.74; H, 1.66; N, 13.91, Found: C, 39.80; H, 1.53; N, 13.99. **E-6**: ^{1}H NMR (DMSO-d_6): δ 10.84 (bs, 1 H, =NH), 10.57 (bs, 1 H, =NH), 8.37 (s, 1 H, aromatic H), 8.18 (s, 1H, aromatic H), 6.42 (s, 1 H, olefinic H); ^{13}C NMR(DMSO-d_6): δ 162.89, 153.48, 146.11, 135.12, 133.70, 132.02, 130.47, 128.42, 125.52, 105.16; *Anal.* Calcd for $C_{10}H_5Cl_2N_3O_4$(302): C, 39.74; H, 1.66; N, 13.91. Found: C, 39.97; H, 1.48; N, 13.70.
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8. **Z-7**: ^{1}H NMR (DMSO-d_6): δ 11.20 (s, 1 H, =NH), 10.60 (s, 1 H, =NH), 7.37 (s, 1 H, aromatic H), 6.88 (s, 1 H, aromatic H), 6.30 (s, 1H, olefinic H), 5.81 (bs, 2 H, -NH_2).
9. **8**: ^{1}H NMR (360 MHz, DMSO-d_6): δ 11.72 (bs, 1H, =NH), 11.28 (bs, 1H, =NH), 8.32 (s, 1H, aromatic H), 8.00 (s, 1H, aromatic H), 7.64 (s, 1H, aromatic H); ^{13}C NMR (360 MHz, DMSO-d_6): δ 155.45, 148.37, 141.85, 128.59, 128.19, 127.94, 126.08, 125.96, 125.54, 109.13; MS (EI) *m/z* 253 (M^+, 100%); *Anal.* Calcd for $C_{10}H_5N_3OCl_2$(254): C, 47.24; H, 1.97; N, 16.53; Found: C, 47.00; H, 2.05; N, 16.39.

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