Condensation of 2-Methylbenzoxazole with Aromatic Aldehydes Bearing Acidic Protons. A Convenient Coupling in the Synthesis of the HIV-Reverse Transcriptase Inhibitor L-696,229

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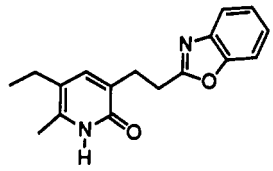
The condensation of methyl-substituted azaheterocyclic compounds with aldehydes has been the focus of synthetic efforts for many years since the resulting alkenyl-substituted heterocycles are useful intermediates for further elaboration as well as components of optical brighteners and dyes.[1] More recently, alkenyl-substituted benzoxazoles and benzothiazoles have been shown to be potentially useful as gastric antisecretory agents.[2]

In the ongoing search for successful therapies for the acquired immune deficiency syndrome (AIDS), we required a practical synthesis of the latest HIV-reverse transcriptase (RT) inhibitor L-696,229 (1).[3a]



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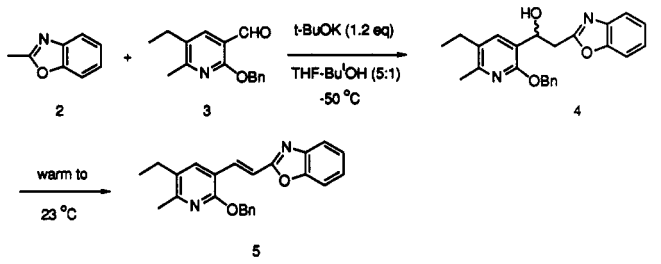
The most direct route that could be envisioned involved the condensation of 2-methylbenzoxazole (2) with the aldehyde 3 to afford the alcohol 4 which upon dehydration would produce the olefin 5 (Scheme I). The latter could be converted to 1 by hydrogenation. Although this appeared to be a straightforward process, a survey of the literature revealed that, unlike oxazolines[4] and benzothiazoles,[5] there are few methods[6] to effect the condensation of 2-methylbenzoxazoles with aromatic aldehydes. Indeed, in our hands, even the most successful procedures reported[7] gave only fair to poor yields of the desired condensation products when the aromatic aldehyde contained alkyl groups at the ortho or para position.

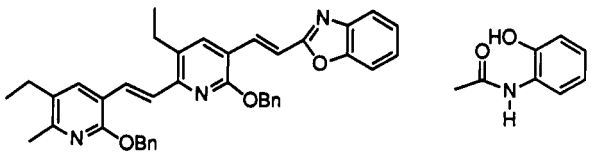
Scheme I



2 3 4 5

We report here a simple, one-step procedure (Scheme I) for the condensation of 2-methylbenzoxazole with aromatic aldehydes, bearing acidic protons at the ortho or para position. These condensations give either the aldol type product (e.g. alcohol 4) or the corresponding dehydration product (e.g. olefin 5) in high yield. The process has been performed on a 60-kg scale and has afforded, after hydrogenation, L-696,229 of ≥99.5% purity.

Attempts to effect the condensation of 2 and 3 by the literature procedures (50% aqueous NaOH in DMSO or 50% aqueous NaOH, in the absence of solvent, with a phase-transfer catalyst)[6c,7] gave poor yields (ca. 40%) of the condensation product. Several impurities were detected by HPLC including product 6 (ca. 20% yield)[8] resulting from initial self-condensation of aldehyde 3[9] and subsequent condensation of 2.



6 7

Moreover, treatment of 2 with n-BuLi or amide bases at −78 °C followed by addition of aldehyde 3 produced moderate yields of 4 along with the methylbenzoxazole decomposition product, amide 7 (detected by HPLC analysis). Control experiments indicated that benzoxazole 2 was unstable under the above reaction conditions as substantial amounts of 7 were formed even at −78 °C. Hoffman et al. have been able to isolate the alcohol 4 in

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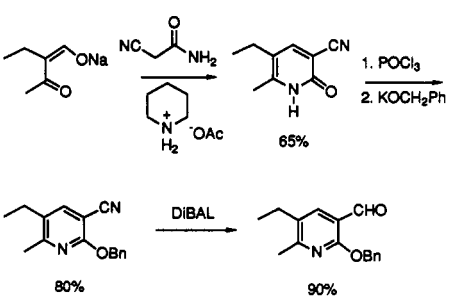
(6) (a) Ried, W.; Hinsching, S.; *Liebigs Ann. Chem.* **1956**, *600*, 43. (b) Dryanska, V.; Ivanon, C. *Tetrahedron Lett.* **1975**, 3519. (c) Dryanska, V.; Ivanon, C. *Synthesis* **1976**, 37.
(7) Lokhande, S. B.; Rangneka, D. W. *Indian J. Chem.* **1986**, *25B*, 485.
(8) (a) Due to overlapping peaks in the aromatic region, identification of 6 was carried out after hydrogenation to the corresponding reduced and debenzylated dipyridone–benzoxazole adduct: ^{1}H δ ($CDCl_3$) 7.67 (m, 1 H), 7.47 (m, 1 H), 7.28 (m, 2 H), 7.21 (s, 1 H), 7.11 (s, 1 H), 3.33 (t, J = 7.4 Hz, 2 H), 3.12 (t, J = 7.6 Hz, 2 H), 2.96 (m, 2 H), 2.80 (m, 2 H), 2.39 (overlapping q, 4 H), 2.32 (s, 3 H), 1.12 (t, J = 7.5 Hz, 3 H), 1.07 (t, J = 7.5 Hz, 3 H); ^{13}C; δ ($CDCl_3$) 167.0, 164.5, 164.3, 150.8, 144.2, 141.6, 141.4, 141.1, 140.0, 128.2, 127.2, 124.4, 124.0, 119.5, 118.7, 118.6, 110.3, 32.3, 29.8, 28.0, 27.6, 23.5, 23.1, 16.1, 15.6, 15.0. (b) The structures of impurities 8–12 were determined from their ^{1}H and ^{13}C NMR data. They are available in the supplementary material (1 page).
(9) The aldehyde 3 was prepared according to the following scheme:



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68% yield by running the condensation with n-BuLi at −100 °C. A number of methylbenzoxazole decomposition products were observed even under those conditions.[3b]

Consequently, in situ trapping of the unstable anion of **2** with the aldehyde was deemed as the best alternative to retard the decomposition. However when a mixture of **2** and **3** was treated with the hindered base lithium tetramethylpiperidide at −78 °C, the condensation product **4** and the starting material **3** were obtained as a 1:1 mixture. This result indicates that deprotonation of the *p*-methyl substituent in **3**, under kinetic conditions, competes with the desired benzoxazole deprotonation–aldehyde condensation sequence. Consequently we sought to effect the condensation under thermodynamic conditions.

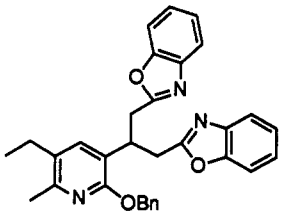
Little success in obtaining clean condensation was achieved under a variety of reaction conditions, with reagents such as DBU, Et_3N, 4-(dimethylamino)pyridine, tetramethylguanidine, Et_3N–$TiCl_4$, NaOMe, Ac_2O–NaOAc, and $FeCl_3$–Ac_2O.

Potassium *tert*-butoxide was found to be the best reagent for this transformation, specifically, when a mixture of **2** and **3** (4:1 molar ratio) in THF–t-BuOH (5:1) was treated with 1.2 equiv of t-BuOK at −50 °C. Under these conditions the anion of **2** was successfully trapped by the aldehyde **3** to give the alcohol **4** which can be isolated in ca. 80% yield by quenching the reaction at −50 °C with aqueous NH_4Cl. Alternatively, warming the reaction mixture to 23 °C for 2 h gave the dehydration product **5** in 82% yield after aqueous workup and crystallization from methanol.[10] Under these conditions only 0.7% of **6** was produced.

Several reaction conditions were investigated and it was discovered that the purity and yield of the condensation product **5** depended on *the temperature, the solvent composition, and the counterion of the base.*

When the condensation was performed at 0 °C to 23 °C, **5** was isolated in 80% yield but the product was contaminated with 3–4% of **6**. Removal of impurity **6** proved difficult since recrystallization was unsuccessful and chromatographic purification was impractical at the multikilogram scale.

Performing the reaction in t-BuOH at 23 °C resulted in a complex reaction mixture while in THF alone (−50 to 23 °C) substantial amounts (≥30%) of the Michael adduct **8** were formed. Nonpolar solvents (eg. $PhCH_3$, hexane)



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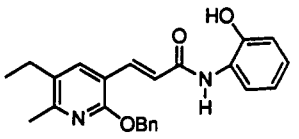

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succeeded in suppressing the formation of **6**; however, unacceptable amounts of the amide **9** were detected. In addition, operational difficulties were encountered with these solvents due to the formation of gels which prevented thorough agitation.

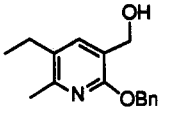
Changing the *tert*-butoxide counterion also gave some interesting results. No condensation was observed with

(10) Solutions of the olefin **5** had to be protected from light since it isomerizes rapidly in solution. The $t_{1/2}$ for this photoisomerization was 6 h in CH_3CN solution.

Table I. Results of *tert*-Butoxide-Induced Condensation of Methylbenzoxazole with Aromatic Aldehydes

aldehyde	base	solvent	temp, °C	product	yield, %
13	t-BuOK	THF–t-BuOH (5:1)	−50 to 23	16	80
13	t-BuOK	THF	−50 to 23	16	58
13	t-BuONa	THF	−50 to 23	16	67
14	t-BuOK	THF–t-BuOH (5:1)	−50 to 23	17	95
15	t-BuOK	THF–t-BuOH (5:1)	−50 to 23	18	82
13	t-BuOK	THF–t-BuOH (5:1)	−50	19	80
15	t-BuOK	THF–t-BuOH (5:1)	0	18	81
14	t-BuOK	THF–t-BuOH (5:1)	0	17	95

t-BuOLi in THF–t-BuOH while a complex reaction mixture, with diminished yields of **5** (~50%), resulted with t-BuONa in the same solvent system. Interestingly, 60% of **5** was obtained with t-BuONa in $PhCH_3$ along with ca. 30% of the Cannizzaro products **10** and **11** and ca. 5–10% of a compound whose ^1H and ^{13}C NMR were



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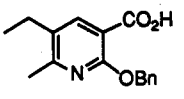

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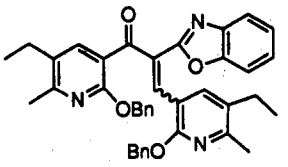

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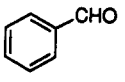
consistent with the structure **12**. The latter could be derived from an Oppenauer-type oxidation of **4** by **3** to give the corresponding β-keto benzoxazole and **10**. The β-keto benzoxazole would further react with **3**, under the reaction conditions, to give **12**.

To demonstrate the generality of the condensation procedure, aldehydes **13**, **14**, and **15** were condensed with 2-methylbenzoxazole with the results shown in Table I. In general, high yields of the olefin were obtained when the reaction was warmed to ambient temperature while the intermediate alcohol could be isolated when the reaction was quenched at −50 °C. Unlike the condensation of aldehyde **3**, the reaction of **2** with **13**, **14**, and **15** to the product olefins **16**, **17**, and **18**, could be performed at 0 °C without loss in yield or product purity. This methodology



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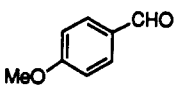

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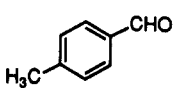

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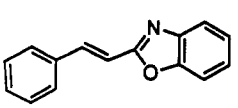

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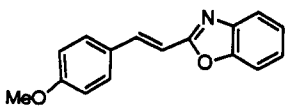

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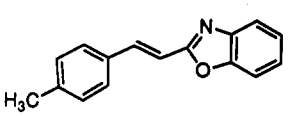

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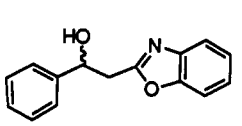

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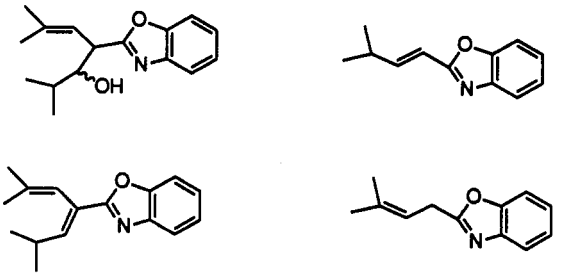
Scheme II



is limited to heterocyclic or aromatic aldehydes since attempts to react 2 with isobutyraldehyde, even under the best reaction conditions, gave the mixture of products shown in Scheme II.

In conclusion, a mild and convenient method for the condensation of heterocyclic and aromatic aldehydes has been described. From an operational standpoint, the reaction is simple and can be performed on multikilogram scale and the product required minimal purification.

Experimental Section

All solvents were dried over 4A molecular sieves to a water content of less than 20 μg/mL as measured by Karl Fisher titration and were used without further purification. The reactions were monitored by reverse-phase HPLC on a Zorbax-RX column, with CH_3CN–H_2O (containing 0.1% H_3PO_4) as eluent, at 210 nm.

General Procedure for Condensation at −50 °C. Preparation of 5. A solution of the aldehyde 3 (5.51 g, 21.6 mmol) and methylbenzoxazole (10.3 mL, 86.4 mmol) in THF (55.5 mL) and t-BuOH (14.5 mL) was cooled to −50 °C under N_2 and treated with a solution of t-BuOK in THF (16.5 mL of 1.7 M solution, 28.08 mmol) at such a rate that the internal reaction temperature did not exceed −46 °C. After 2 h at −50 °C, HPLC analysis indicated <0.3% of the aldehyde remained. The cooling bath was removed and the mixture was stirred at ambient temperature for 12 h in the dark. Aqueous $NaHCO_3$ (55 mL) and toluene (55 mL) were added. The organic layer was washed with 10% aqueous NaCl (55 mL) and subsequently treated with Calgon Rb-type pulverized carbon (1.2 g) with agitation for 3 h. Filtration through Celite, concentration in vacuo, and recrystallization from MeOH (70 mL) afforded 5 in 82% yield (6.55 g). HPLC analysis (gradient elution 65:35 CH_3CN–H_2O to 100:0 CH_3CN–H_2O in 35 min at 210 nm) indicated the product was >97% pure. An analytical sample was obtained by preparative TLC (9:1 ethyl acetate–hexanes): ^1H NMR ($CDCl_3$) δ 7.93 (d, J = 16.5 Hz, 1 H), 7.71 (m, 1 H), 7.56 (m, 2 H), 7.51 (m, 1 H), 7.41 (m, 2 H), 7.32 (m, 4 H), 7.26 (d, J = 16.5 Hz, 1 H), 5.55 (s, 2 H), 2.61 (q, J = 7.6 Hz, 2 H), 2.47 (s, 3 H), 1.23 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.3, 158.5, 155.1, 150.4, 142.2, 137.7, 137.3, 134.2, 130.2, 128.4, 128.1, 127.7, 124.9, 124.3, 119.7, 115.6, 114.8, 110.3, 67.5, 24.7, 21.7, 14.3. Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.82; H, 5.99; N, 7.56. Found: C, 77.55; H, 6.05; N, 7.39.

4: ^1H NMR ($CDCl_3$) δ 7.67 (m, 1 H), 7.52 (s, 1 H), 7.45 (m, 3 H), 7.33 (m, 5 H), 5.45 (m, 1 H), 5.43 (s, 2 H), 4.1 (br. s, 1 H), 3.48 (dd, J_1 = 3.7; J_2 = 15.9 Hz, 1 H), 3.26 (dd, J_1 = 8.6; J_2 = 15.9 Hz, 1 H), 2.55 (q, J = 7.6 Hz, 2 H), 2.42 (s, 3 H), 1.15 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.9, 137.8, 135.8, 130.1, 128.4, 128.0, 127.7, 124.8, 124.3, 121.6, 119.6, 110.5, 67.3, 66.9, 36.1, 24.9, 21.3, 14.5; IR (cm^{-1}, $CHCl_3$) 3480, 3070, 3040, 2980, 1610, 1575, 1455, 1440, 1340, 1240, 1150, 1050, 1010.

Preparation of 19. A solution of benzaldehyde (3.89 g, 36.72 mmol) and methylbenzoxazole (5.15 mL, 44.06 mmol) in THF (99 mL) and t-BuOH (19.8 mL) was cooled to −50 °C under N_2 and treated with a solution of t-BuOK in THF (28.08 mL of 1.7 M solution, 47.74 mmol) with the internal reaction temperature not exceeding −46 °C. After 2 h at −50 °C, HPLC analysis indicated <0.2% of the aldehyde remained. The reaction mixture was quenched with aqueous $NaHCO_3$ and partitioned between ethyl acetate and 10% aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous NaCl and concentrated in vacuo. Methanol (120 mL) was added and the mixture heated to 60 °C until complete dissolution of the solid was observed. The solution was cooled to ambient temperature and H_2O was added (60 mL). The resulting solid was filtered, and the crystals were washed with aqueous methanol (2:1 MeOH–H_2O) and then dried in vacuo at 40 °C, to give 6.96 g of 19 (80%): mp 159–159.5 °C (lit. 160–161 °C).[6c]

General Procedure for Condensation at 0 °C. Preparation of 18. A solution of 15 (2.038 g, 16.96 mmol) and 2-methylbenzoxazole (8.05 mL, 67.84 mmol) in THF (46 mL) and t-BuOH (9.2 mL) was cooled to −3 °C under N_2. A solution of t-BuOK in THF (12.97 mL of a 1.7 M solution, 22.05 mmol) was added at such a rate that the temperature did not exceed 0 °C. The reaction was aged at 0 °C for 2 h, warmed to ambient temperature, and then aged for 12 h. Workup as described above produced a solid that was recrystallized by dissolution in MeOH (49 mL) at 65 °C followed by cooling to 28 °C and addition of H_2O (25 mL). Filtration and drying of the solid afforded 3.2 g (82%) of 18: HPLC purity >99.5% at 210 nm, mp 128–129 °C (lit. 130–132).[6c] 16 [mp 81.5–82 °C (lit. 82 °C)[6c]] and 17 [mp 135–136 °C (lit. 136–137 °C)[6c]] were prepared in a similar manner.

Supplementary Material Available: ^1H and ^{13}C NMR spectral data for compounds 8–12 (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.