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An Improved Process for the Synthesis of 4*H*-Imidazo[1,5-*a*][1,4]benzodiazepines

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Abstract

The construction of CNS active imidazo[1,5-a][1,4]benzodiazepines has been improved in a one-pot annulation process.

Keywords

$GABA_A$/BzR; imidazo[1,5-a][1,4]benzodiazepines; ethyl isocyanoacetate; annulation

Introduction

Imidazo[1,5-a][1,4]benzodiazepines are well docmented to exhibit potent activity at $GABA_A$/Bz receptors. This series belongs to one of the very few chemical families which have been extensively investigated for $GABA_A$/Bz receptor mediated activity.1,2 Flumazenil (Ro 15-1788), an imidazo[1,5-a][1,4]benzodiazepine, was earlier shown to bind to central $GABA_A$ receptors with little or no intrinsic agonist activity but with the ability to block the activity of an agonist or inverse agonist at $GABA_A$/Bz receptors.2 It is employed principally as an antidote to reverse the effect of exogenous benzodiazepines.3 More recently ligands such as flumazenil have been shown to behave as weak inverse agonists or weak agonists depending on the biological paradigm employed. Many procedures have been reported to date to synthesize this imidazo-type of structure.4,5 Most of them have been achieved in low yield through an iminophosphate/chloride intermediate.

As part of a program directed toward the development of clinically relevant imidazo[1,5-a][1,4]-benzodiazepines,1,6 the construction of the imidazo-ring was considered a crucial step for the synthesis of gram quantities of imidazobenzodiazepine analogs. The previous process of using ethyl isocyanoacetate and iminophosphates/chlorides7,8 was employed coupled with different solvents and bases, but the yields of these reactions were very low (15–30%). Since this step was highly convergent and at the very end of the synthetic route, it affected the overall economy of the route in a dilatorious manner. It was, therefore, of interest to improve the annulation sequence for this series of CNS-active ligands.

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Certainly a one-pot annulation process for the construction of imidazobenzodiazepines had been developed.(7,8) This procedure permited the condensation of the less stable iminophosphates with ethyl isocyanoacetate under basic conditions without isolation of the less stable iminophosphates and the pre-formation of the carbanion of ethyl isocyanoacetate. For instance, Watjen et al.7a had reported the formation of iminophosphates by using NaH or LDA in DMF, and then directly reacting this mixture with ethyl isocyanoacetate and potassium *tert*-butoxide to offer the imidazo molecules in 47% yield. Fryer and coworkers7b,c had reported the use of potassium *tert*-butoxide as the base in both steps, and DMF as well as THF were chosen as solvents in these cases; however, this process gave the ligands in only 44% yield. The latest report from Fryer's procedure gave the target imidazo framework in 30% yield.8

Scope and Limitations

To improve the one-pot annulation reaction, the procedure was modified and after many attempts it was found the ratio of the reagent combination and reaction temperature were critical for good yields on a consistent basis. As shown in scheme 1, the initial amount of potassium *tert*-butoxide used to form the iminophosphates should be kept at 1.1 equivalents as compared to the amide (**1a–k**). The yield of the reaction was much lower if more potassium *tert*-butoxide (>1.1 equ-ivalents) was employed. The amount of diethylchlorophosphate (used as received) employed was only slightly higher (1.3 equivalents) than the potassium *tert*-butoxide to convert all the starting amide into the desired iminophosphates (**1a–k**). Importantly, the addition of ethyl isocyanoacetate, followed by the second addition of potassium *tert*-butoxide should be carried out at low temperature (−35 °C is recommended). However, a temperature lower than −35 °C (such as −78 °C) was also acceptable in this procedure and the second addition of potassium *tert*-butoxide was kept at 1.1 equivalents. This procedure made the separation of the product much easier which was critical for gram scale reactions. Most of the desired imidazobenzodiazepines were precipitated from ether after work-up for no chromatography was needed.

A variety of different amidobenzodiazepines (**1a–h**) were chosen as substrates for this study (See Table-1). Both the 5-phenyl-benzodiazepines (**1a–f**) and N-methyl-6-oxo-benzodiazepines (**1g–h**) readily condensed with ethyl isocyanoacetate to give the desired imidazobenzodiazepines (**3a–k**) in 70–89% yield in this improved process. The substituents in ring-A such as F, Cl, Br of **1a–h** did not effect the yield of the process. The α-substituted amidobenzodiazepines (**1c–e**, and **1i**), which are more hindered than their unsubstituted parents (**1a–b** and **1f–1j**), also gave the imidazo analogs in 70–81% yield. In the case of optically active substrates (**1c–e**, and **1i**), this procedure provided the desired imidazo products without loss in optical activity. This is key for the *R* and *S* isomers have much different BzR/GABAergic receptor binding profiles. All of these reactions can be scaled up with no difficulty. The lesser amounts of **3d–3g** simply reflect the lesser need for this material. When this process was employed for reactions of *tert*-butyl isocyanoacetate, the corresponding imidazobenzodiazepines were obtained in 70% yield.

An efficient, practical, improved, one-pot annulation reaction for the construction of potent BzR active imidazobenzodiazepines is described. A variety of substrates were successfully employed in this procedure. This one-pot process required neither the isolation of the unstable intermediates nor does it require the pre-formation of the carbanion of the isocyanocetate. Moreover, potassium *tert*-butoxide is a safer and easier-to-handle base for scale-up, as compared to other bases such as NaH, LHMDS and LDA. In addition, no chromatography was required for this process.

General procedure for synthesis of imidazo[1,5-a][1,4]benzodiazepines

Potassium *t*-butoxide (1.1 mmol) was added to a solution of the amidobenzodiazepine (1.0 mmol) in THF (20 mL) at 0 °C under argon. After stirring the mixture at 0 °C for 20 min, the reaction mixture was cooled to −35 °C and diethylchlorophosphate (1.3 mmol) was added slowly. After stirring this mixture at 0 °C for 30 min, the reaction flask was cooled to −35 °C and ethyl isocyanoacetate (1.1 mmol) was added, followed by addition of potassium *t*-butoxide (1.1 mmol). After stirring this mixture at ambient temperature for 4 hours, the reaction solution was quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were dried (Na_2SO_4), concentrated and precipitated from ether to give most of the imidazobenzodiazepine. The mother liquor was purified by flash chromatography on silica gel (40–60 % EtOAc in hexanes) to afford additional imidazobenzodiazepine (yields 70–89%).

Scale up procedure for synthesis of imidazo[1,5-a][1,4]benzodiazepines

Potassium *t*-butoxide (7.5g, 66.91 mmol) was added to a solution of **1j** (15g, 55.76 mmol) in 1500mL anhydrous THF at 0°C and stirred for 20 min. The reaction mixture was cooled to −35°C and diethylchlorophosphate (12.5-mL, 72.49 mmol) was added slowly. After stirring at 0°C for 30 min, the reaction mixture was cooled to −78°C and ethyl isocyanoacetate (8.19mL, 72.49 mmol) was added followed by the addition of potassium *t*-butoxide (6.88g, 61.33 mmol). After stirring at room temperature for 4h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to get a solid residue. This solid residue was treated with ether and the product **3j** was precipitated as an off-white solid. The mother liquor was further purified by flash chromatography on silica gel (gradient elution 40–60% EtOAc in hexane) to afford additional product **3j** with overall yield of 72% (14.61g).

Ethyl-8-chloro-6-phenyl-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (3a)

Mp: 180–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.68 (dd, 1H, *J* = 2.3, 2.3 Hz), 7.58 (s, 1H), 7.55-7.37 (m, 6H), 6.06 (d, 1H, *J* = 12.3 Hz), 4.70 (m, 2H), 4.15 (d, 1H, *J* = 14Hz), 1.46 (t, 3H). HRMS for $C_{20}H_{16}ClN_3O_2$: (M+1) 366.1007. Found: 366.1000.

Ethyl-8-bromo-6-phenyl-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (3b)

Mp: 180–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.82 (dd, 1H, *J* = 2.2, 8.6 Hz), 7.60 (d, 1H, *J* = 2.2Hz), 7.53-7.40 (m, 6H), 6.08 (d, 1H, *J* = 12.3 Hz), 4.49-4.38 (m, 2H), 4.09 (d, 1H, *J* = 12.1 Hz), 1.44 (t, 3H, *J* = 7.1Hz). EIMS m/e (relative intensity, %) 411

(M+1, 34), 410 (M^+, 8), 409 (34), 365 (61), 337 (100), 335 (100), 285 (21), 232 (17). Anal. Calcd. for $C_{20}H_{16}BrN_3O_2$: C, 58.55; H, 3.93; N, 10.24. Found: C, 58.30; H, 3.91; N, 9.94.

(*R*)-Ethyl-8-bromo-4-methyl-6-(2′fluorophenyl)-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (3c)

White solid. Mp: 261–262 °C. $[\alpha]_D^{25}$ −10.9 (c, 0.54, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.72 (dd, 1H, *J* = 1.5, 8.2 Hz), 7.60 (t, 1H, *J* = 6.9 Hz), 7.48 (d, 1H, *J* = 8.5 Hz), 7.49-7.42 (m, 2H), 7.29-7.23 (m, 1H), 7.05 (t, 1H, *J* = 9.3 Hz), 6.71 (q, 1H, *J* = 7.3 Hz), 4.41 (m, 2H), 1.42 (t, 3H, *J* = 7.1 Hz), 1.29 (d, 3H, *J* = 7.2 Hz). EIMS m/e (relative intensity, %) 442 (M+, 5), 428 (7), 381 (58), 355 (100). Anal. Calcd. for $C_{21}H_{17}BrFN_3O_2$: C, 57.03; H, 3.87; N, 9.50. Found: C, 57.13; H, 3.89; N, 9.51.

(*R*)-Ethyl-8-bromo-4-ethyl-6-(2′-fluorophenyl)-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate(3d)

White solid. Mp: 253–254 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.72 (dd, 1H, *J* = 8.1 Hz), 7.59 (t, 1H, *J* = 7.5 Hz), 7.48-7.42 (m, 2H), 7.28-7.23 (m, 1H), 7.06 (t, 1H, *J* = 9.3 Hz), 6.51 (q, 1H, *J* = 7.8 Hz), 4.43 (m, 2 H), 1.76-1.52 (m, 3H), 1.43 (t, 3H, *J* = 7.2 Hz), 0.96 (t, 3H, *J* = 7.2 Hz). HRMS Calcd. for $C_{22}H_{19}BrFN_3O_2$: 456.0723; Found: 456.0709.

(*S*)-Ethyl-8-bromo-4-ethyl-6-(2′-fluorophenyl)-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (3e)

White solid. Mp: 254–255 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.72 (dd, 1H, *J* = 7.2 Hz), 7.59 (t, 1H, *J* = 6.9 Hz), 7.48-7.41 (m, 2H), 7.28-7.23 (m, 1H), 7.06 (t, 1H, *J* = 9.3 Hz), 6.51 (m, 1H), 4.45-4.37 (m,2H), 1.75-1.54 (m,3H), 1.42 (t, 3H, *J* = 6.9 Hz), 0.94 (t, 3H, *J* = 7.2 Hz). HRMS Calcd. for $C_{22}H_{19}BrFN_3O_2$: 456.0723; Found: 456.0703.

Ethyl-7-bromo-6-phenyl-4*H*-imidazo[1,5-a]-thieno-[2,3-f][1,4]diazepine-3-carboxylate(3f)

White solid. Mp: 180–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 8.02 (s, 1H), 7.63-7.35 (m, 5 H), 5.31 (s, 2H), 4.34-4.27 (q, 2H, *J* = 7.1 Hz), 1.32 (t, 3H, *J* = 7.1 Hz). HRMS for $C_{18}H_{14}BrN_3O_2S$: 416.0068. Found: 416.0049.

Ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (3g)

Off-white solid. Mp: 200–202 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.81-7.78 (m, 1H), 7.74-7.36 (m, 2H), 5.25 (br s, 1H), 4.44 (q, 2H, *J* = 7.3 Hz), 4.38 (br s, 1H), 3.27 (s, 3H), 1.47 (t, 3H, *J* = 7.3 Hz). HRMS for $C_{15}H_{14}FN_3O_3$: (M+1) 304.1097. Found: 304.1091. The spectral data for **3g** were identical to the published values.2,4

Ethyl-8-chloro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (3h)

Mp: 200–202 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.90 (s, 1H), 7.62 (dd, 1H, *J* = 8.6, 2.5 Hz), 7.40 (d, 1H, *J* = 8.6 Hz), 5.23 (br s, 1H), 4.46 (q, 2H, *J* = 7.1 Hz), 4.13 (br s, 1H), 3.27 (s, 3H), 1.47 (t, 3H, *J* = 7.1 Hz).). EIMS for $C_{15}H_{14}ClN_3O_2$: m/e (relative intensity, %) 319 (M^+, 100).

(*S*)-Ethyl 7-bromo-11,12,13,13a-tetrahydro-9-oxo-9*H*-imidazo[1,5-*a*]pyrrolo[2,1-*d*][1,4]benzodiazepine-1-carboxylate (3i)

White solid. Mp: 248.5–249 °C; $[\alpha]_D^{25}$+45 (c, 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.82 (s, 1H), 7.75 (d, 1H, *J* = 7.5 Hz), 7.26 (d, 1H, *J* = 10.0 Hz), 4.72 (d, 1H, *J* = 6.0 Hz), 4.38 (q, 2H, *J* = 7.5 Hz), 3.75 (m, 1H), 3.56-3.48 (m, 2H), 2.27-2.14 (m, 3H), 1.41 (t, 3H, *J* = 7.5 Hz). EIMS m/e (relative intensity, %) 390 (M^+, 10), 345 (60), 316 (100), 314 (98), 154 (24). Anal. Calcd. for $C_{17}H_{16}BrN_3O_3$: C, 52.32; H, 4.13; N, 10.77. Found: C, 52.70; H, 4.48; N, 10.64. HRMS for $C_{17}H_{16}BrN_3O_3$: 389.0375. Found: 389.0373.

Ethyl-8-bromo-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (3j)

Off-white solid. Mp: 192–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.79 (s, 1H), 7.77 (d, 1H, *J* = 2.3 Hz), 7.35 (d, 1H, *J* = 6.4 Hz), 5.17 (br s, 1H), 4.43 (m, 3H), 3.28 (s, 3H), 1.45 (t, 3H, *J* = 7.1 Hz). EIMS for $C_{15}H_{14}BrN_3O_3$: m/e (relative intensity, %) 364 (M^+, 100).

tert-Butyl-8-bromo-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (3k)

Mp: 180–183 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 1H), 7.92 (s, 1H), 7.69 (d, 1H, *J* = 10.8 Hz), 7.03 (d, 1H, *J* = 8.7 Hz), 4.71 (br s, 1H), 4.12 (br s, 1H), 3.10 (s, 3H), 1.56 (s, 9H). EIMS for $C_{17}H_{18}BrN_3O_3$: m/e (relative intensity, %) 394 (M^+, 100).

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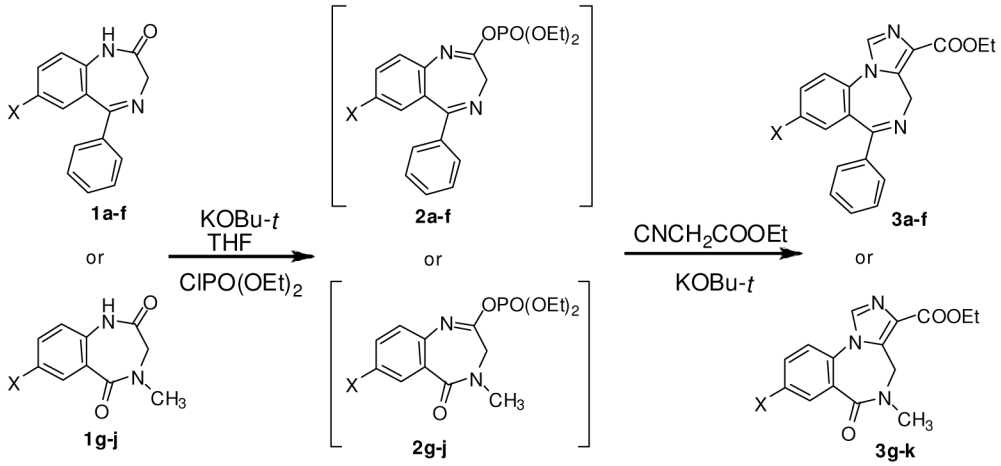
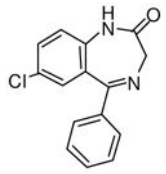
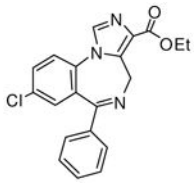
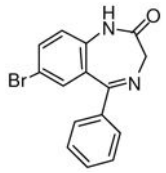
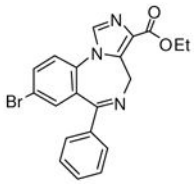
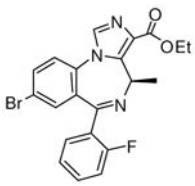
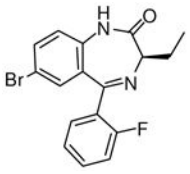
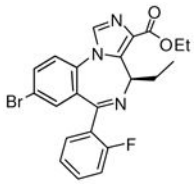
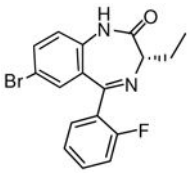
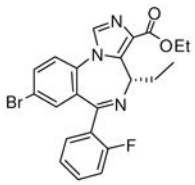
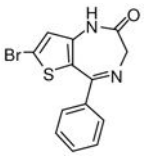
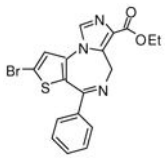
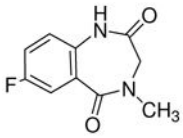
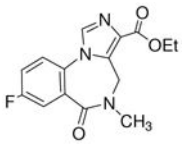
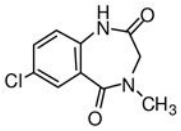
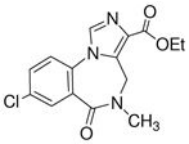
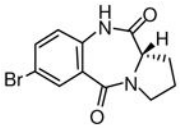
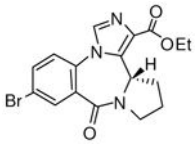
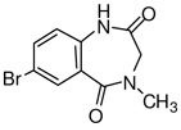
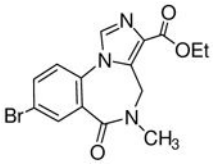
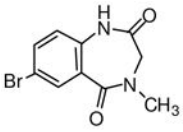
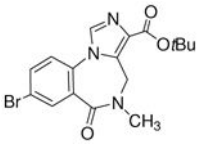


Scheme 1.

Table 1

Examples of Imidazo[1,5-a][1,4]benzodiazepines Obtained Using the General Procedure

Starting material	Product	Yield (%) Scale
 **1a**	 **3a**	87 (11 g scale)
 **1b**	 **3b**	77 (15 g scale)
 **1c**	 **3c**	74 (10 g scale)
 **1d**	 **3d**	73 (3.6 g scale)
 **1e**	 **3e**	72 (1 g scale)
 **1f**	 **3f**	75 (5 g scale)

Starting material	Product	Yield (%) Scale
 **1g**	 **3g**	75 (2 g scale)
 **1h**	 **3h**	89 (15 g scale)
 **1i**	 **3i**	81 (15 g scale)
 **1j**	 **3j**	72 (15 g scale)
 **1k**	 **3k**	70 (20 g scale)