

Research Article

A Simple and Advantageous Synthesis of the Privileged 1,4-Benzodiazepine Nucleus

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A novel domino approach has been described for an easy access of the privileged nucleus of 5-carbomethoxy substituted 1,4-benzodiazepin-2-ones **4(a-i)** from an in situ methanolic hydrolysis of an incipient species formed from the interaction of 1-chloroacetylisatin **2(a-i)**, hexamethyldisilazane, and *n*-butyl lithium. The reaction is believed to take place through a consecutive series of intramolecular reactions in a cascade to first generate a highly reactive carbene intermediate **3(a-i)** from 1-chloroacetylisatin and *n*-butyl lithium which is simultaneously trapped by hexamethyldisilazane before undergoing its in situ hydrolysis with methanol to initiate its concomitant cyclocondensation to produce **4(a-i)** in high yield and purity.

1. Introduction

Exploration of synthetic processes that lead to the development of small molecules of medicinal interest by telescoping the multicomponent operations into a single step or resorting to a process such as domino reactions is a rapidly emerging subject in medicinal chemistry. Ever since Koch et al. [1] carried out a quantitative analysis of physiologically active natural product scaffolds and showed that ones with two or three rings were most often found in bioactive natural products, the interest on various facets of the chemistry of small molecules has expanded exponentially thereafter. Benzodiazepines and their analogues have been recognized recently to belong to the class of privileged heterocyclic structures, [2–5] by virtue of their ability to form ligands to a number of functionally and structurally discrete biological receptors [6–13]. This property stimulated chemists to utilize their potential in the design and development of molecular probes for biological evaluations. Ubiquitous presence of this nucleus in the psychopharmacologically active agents and in molecules active against HIV infection, for example, TIBO (1) [14–17] and FDA approved dipyrrolo diazepine analogue nevirapine (2) [18–24] in Figure 1 provided an impetus for an enormous research effort to be directed towards

the development of their structural analogues of medicinal importance [25, 26].

2. Results and Discussion

This communication reports the application of a novel domino process for an easy access of the privileged nucleus of 5-carbomethoxy substituted 1,4-benzodiazepin-2-ones **4(a-i)** from the ring expansion of 1-chloroacetylisatins **2(a-i)**, initiated by hexamethyldisilazane under the influence of *n*-butyl lithium. *N*-Butyl lithium formed an obvious choice since it has been used as a catalyst in amination of active alkyl halides with hexamethyldisilazane. Amination of 1-chloroacetylisatin (**2**) formed the key step in allowing it to undergo ring expansion to give **4**. Ogata and Matsumoto's [27] original procedure which employed Delepine reaction in the amination of **2** with methanolic solution of hexamine produced **4** in low yield. This called out to revisit this reaction to augment the scope of this reaction in view of the yield of this product.

It is believed that Delepine reaction proceeded with the formation of the hexaminium ion. We surmise that it was the bulky nature of hexamine which hindered its formation

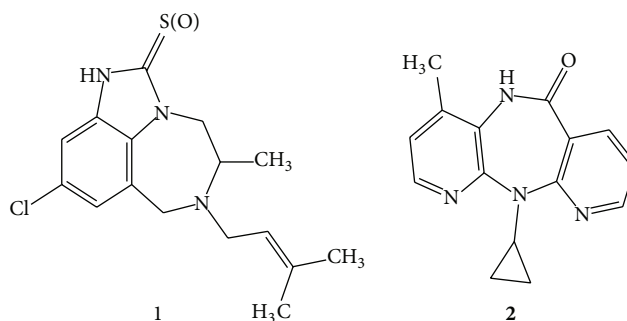


FIGURE 1

from **2**. We assumed that this problem could possibly be circumvented by carrying out the amination of **2** with less bulkier agents. In consideration of the potential of hexamethyldisilazane [28] in amination reaction, in our initial attempt, we replaced hexamine with this reagent. However, contrary to our expectation, **2** resisted its reaction with this reagent and caused it to be recovered unchanged from the reaction mixture. A search for possible use of a catalyst in this reaction revealed that *n*-butyl lithium has been used in aminations employing hexamethyldisilazane. This provided optimism for this reaction too, to succeed with the use of this catalyst. This expectation turned into a reality in all the runs using a wide variety of substituted 1-chloroacetylisatin derivatives to produce **4** in an exceptionally high yield and purity (Table 1).

We suggest that this reaction proceeds with the base catalysed dehydrochlorination of **2** to generate an acyl carbene intermediate **3** which is subsequently trapped by hexamethyldisilazane. The relatively small size of carbene precludes the steric factor in the reaction with hexamethyldisilazane. The hydrolysis of bis(trimethylsilyl) group from this with methanol sets the stage for it, to undergo ring expansion to give **4**.

In view of the extremely weak nucleophilic character of isatinyamide nitrogen of **3**, the possibility of the rearrangement of the acyl carbene intermediate had to be ruled out. (No rearranged product was, however, traceable from the reaction mixture.)

As the carbene was not likely to be trapped by the tertiary amine (hexamine) its reaction with hexamine was not examined.

3. Experiment

All the melting points were taken in open capillaries and are uncorrected. The purity of all the compounds were checked by TLC using the solvent systems (benzene: methanol, 9:1 v/v) and silica gel G as adsorbent. IR spectra were recorded on Shimadzu FTIR-8400 infrared spectrometer using KBr, ^1H NMR were recorded on Bruker AC 300F in CDCl_3 + $\text{DMSO}-d_6$ (2:1 v/v, TMS as internal reference and chemical shifts expressed in δ ppm), and mass spectra

were recorded on Jeol-JMS-D-D-300 mass spectrometer. Reagents, 5-fluoro-, 5-chloro-, 5-bromo-, 5-iodo-, 5-methyl-, 5-methoxy-, 5-nitro-, and 5,7-dimethylisatins were procured from commercial sources and used as such in the reaction without further purifications (see Scheme 1).

3.1. General Methods for the Preparation of 2(a–i) from 1(a–i). 5-Fluoroisatin (**1b**, 0.068 mol) was vigorously refluxed with chloroacetyl chloride (0.090 mol) for 7 h. and the mixture was cooled overnight at 0–5°C. The crude product which settled was filtered, washed with 20 mL of ether, air-dried, and then recrystallised from ethyl acetate to give **2b**, yield: 88%, m.p. 165–166°C. Other compounds **2(a, c–i)** were prepared from **1(a, c–i)** using this procedure.

3.2. General Methods for the Preparation of 4(a–i) from 2(a–i). 5-Fluoro-1-chloroacetylisatin (**2b**, 0.01 mol) was dissolved in dry THF (20 mL) and to this solution *n*-butyl lithium (0.01 mol) and hexamethyldisilazane (0.01 mol) were added. The reaction mixture was magnetically stirred for 2 h at room temperature. The progress of reaction was checked by TLC. Methanol (20 mL) was added to the reaction mass and the mixture was refluxed for 5 h. It was then poured on crushed ice, filtered, air-dried, and recrystallised from methanol to give **4b**, yield: 87%, m.p. 198–200°C. Other compounds **4(a, c–i)** were prepared from **2(a, c–i)** using the same procedure.

4. Conclusion

In summary, a high yielding *n*-butyl lithium catalysed one-pot domino process has been developed to the facile access of the privileged nucleus of methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one-5-carboxylates **4(a–i)** at ambient temperature from the ring expansion of the corresponding 1-chloroacetylisatins **2(a–i)** under the influence of hexamethyldisilazane.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

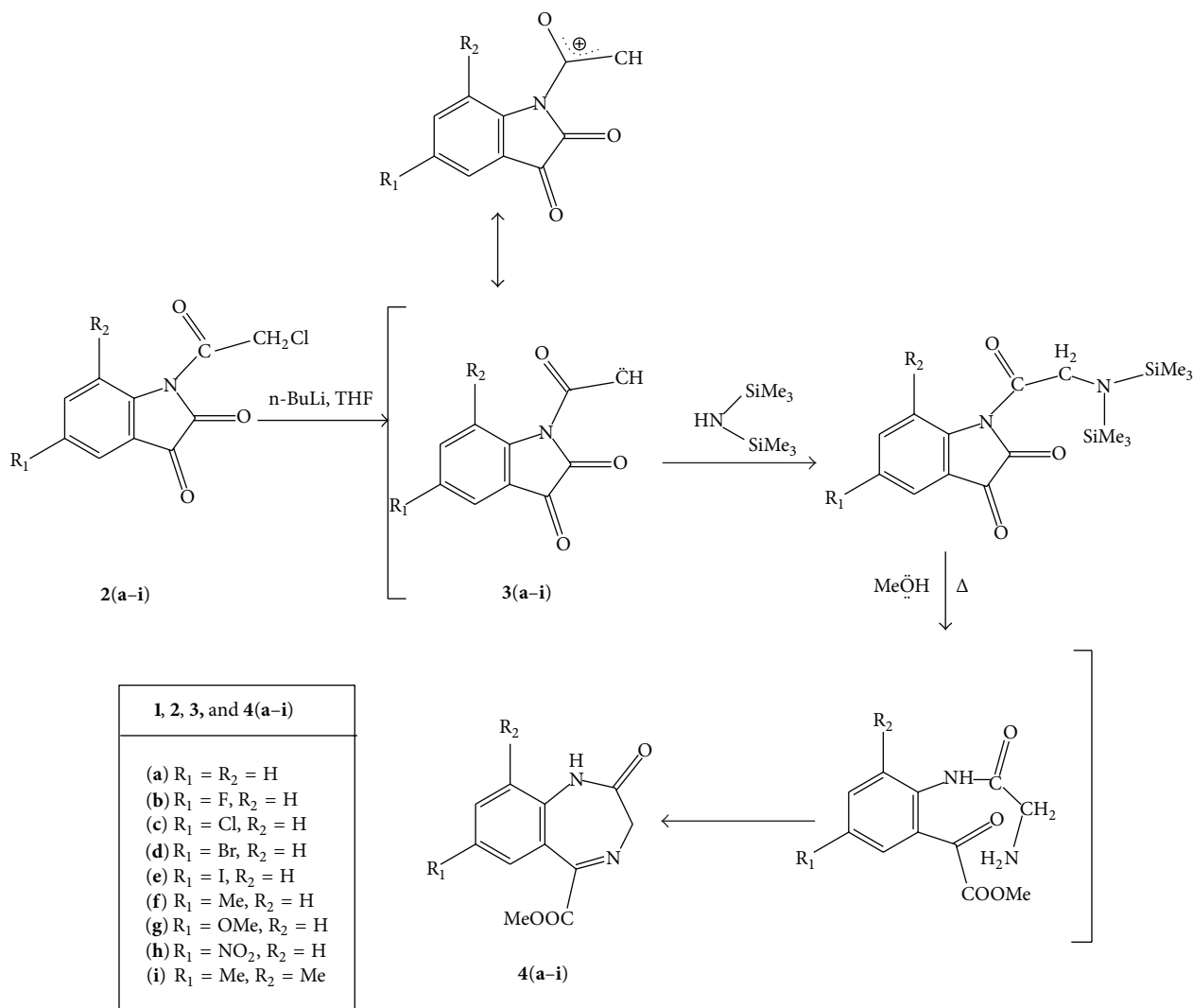
TABLE I: Physical and spectral data of the compounds **2(a-i)** and **4(a-i)**.

Entry	Molecular formula	M.W.	M.P. (°C) ^a	Yield (%)	IR (KBr) cm ⁻¹	¹ H NMR (CDCl ₃ -DMSO-d ₆) δ ppm	C (cald/exp.)	H (cald/exp.)	N (cald/exp.)
2a	C ₁₀ H ₆ ClNO ₃	223.61	210–12	91	1735, 1680, 1675	7.56–7.19 (m, 4H, ArH), 4.32 (s, 2H, CH ₂)	53.71/53.67	2.70/2.65	6.26/6.18
2b	C ₁₀ H ₅ ClFNO ₃	241.60	165–66	88	1755, 1725, 1700	7.81–7.23 (m, 3H, ArH), 4.33 (s, 2H, CH ₂)	49.71/49.67	2.49/2.40	5.80/5.69
2c	C ₁₀ H ₅ Cl ₂ NO ₃	258.06	153–55	94	1785, 1740, 1720	7.81–7.53 (m, 3H, ArH), 4.32 (s, 2H, CH ₂)	46.54/46.42	1.95/1.90	5.43/5.31
2d	C ₁₀ H ₅ BrClNO ₃	302.51	178–79	90	1780, 1735, 1710	7.96–7.61 (m, 3H, ArH), 4.32 (s, 2H, CH ₂)	39.70/39.62	1.67/1.56	4.63/4.59
2e	C ₁₀ H ₅ ClINO ₃	349.51	206–07	89	1770, 1725, 1690	7.80–7.50 (m, 3H, ArH), 4.28 (s, 2H, CH ₂)	28.95/28.89	1.21/1.17	3.38/3.27
2f	C ₁₁ H ₈ ClNO ₃	237.64	185–86	92	1765, 1720, 1690	7.72–7.03 (m, 3H, ArH), 4.32 (s, 2H, CH ₂), 2.85 (s, 3H, CH ₃)	55.60/55.51	3.39/3.28	5.89/5.80
2g	C ₁₁ H ₈ ClNO ₄	253.64	223–25	90	1780, 1740, 1705	3.73 (s, 3H, OCH ₃)	52.09/51.97	3.18/3.12	5.52/5.42
2h	C ₁₀ H ₅ ClN ₂ O ₅	268.61	130–32	91	1785, 1745, 1710	8.72–8.09 (m, 3H, ArH), 4.52 (s, 2H, CH ₂)	44.71/44.56	1.88/1.71	10.43/10.37
2i	C ₁₂ H ₁₀ ClNO ₃	251.67	168–70	92	1740, 1700, 1685	7.40–7.12 (m, 2H, ArH), 4.32 (s, 2H, CH ₂), 2.35 (s, 6H, CH ₃)	57.27/57.19	4.01/3.97	5.57/5.46
4a	C ₁₁ H ₁₀ N ₂ O ₃	218.21	172–75	85	3190, 1725, 1675	8.0 (s, 1H, NH), 7.98–7.65 (m, 4H, ArH), 4.48 (s, 2H, CH ₂), 3.65 (s, 3H, OCH ₃) MS: <i>m/z</i> (%) 218.21 (M+, 100%), 210.20 (75%), 107.16 (35%)	60.55/60.48	4.62/4.52	12.84/12.79
4b	C ₁₁ H ₉ FN ₂ O ₃	236.20	198–200	87	3220, 1735, 1690	8.2 (s, 1H, NH), 8.08 (d, 1H, ArH), 7.78 (d, 1H, ArH), 7.66 (s, 1H, ArH), 4.56 (s, 2H, CH ₂), 3.78 (s, 3H, OCH ₃) MS: <i>m/z</i> (%) 236.20 (M+ 75%), 205.17 (100%), 177.16 (35%)	55.93/55.88	3.84/3.79	11.86/11.76
4c	C ₁₁ H ₉ ClN ₂ O ₃	252.65	176–78	84	3215, 1728, 1684	8.1 (s, 1H, NH), 7.90 (s, 1H, ArH), 7.81 (d, 1H, ArH), 7.60 (d, 1H, ArH), 4.48 (s, 2H, CH ₂), 3.70 (s, 3H, OCH ₃) MS: <i>m/z</i> (%) 252.65 (M+, 100%), 254.57 (M+2, 33%)	52.29/52.23	3.59/3.51	11.09/11.00
4d	C ₁₁ H ₉ BrN ₂ O ₃	297.98	243–45	86	3208, 1721, 1675	8.0 (s, 1H, NH), 7.90 (s, 1H, ArH), 7.75 (d, 1H, ArH), 7.50 (d, 1H, ArH), 4.32 (s, 2H, CH ₂), 3.12 (s, 3H, OCH ₃) MS: <i>m/z</i> (%) 297.98 (M+, 100%), 299.90 (M+2, 100%), 177.16 (35%)	44.47/44.41	3.05/2.99	9.43/9.36
4e	C ₁₁ H ₉ IN ₂ O ₃	344.11	187–88	90	3200, 1710, 1670	8.0 (s, 1H, NH), 7.85 (s, 1H, ArH), 7.66 (d, 1H, ArH), 7.40 (d, 1H, ArH), 4.32 (s, 2H, CH ₂), 3.12 (s, 3H, OCH ₃) MS: <i>m/z</i> (%) 344.11 (M+ 75%), 205.17 (100%), 147.16 (35%)	38.39/38.29	2.64/2.59	8.14/8.07

TABLE I: Continued.

Entry	Molecular formula	M.W.	M.P. (°C) ^a	Yield (%)	IR (KBr) cm ⁻¹	¹ H NMR (CDCl ₃ -DMSO-d ₆) δ ppm	C (cald/exp.)	Elemental analysis H (cald/exp.)	N (cald/exp.)
4f	C ₁₂ H ₁₂ N ₂ O ₃	232.24	205–06	85	3188, 1723, 1672	8.0 (s, 1H, NH), 7.84 (s, 1H, ArH), 7.56 (d, 1H, ArH), 7.42 (d, 1H, ArH), 4.32 (s, 2H, CH ₂), 3.12 (s, 3H, OCH ₃), 2.34 (s, 3H, CH ₃) MS: <i>m/z</i> (%) 232.24 (M + 72%), 177.25 (25%), 149.17 (100%) 8.0 (s, 1H, NH), 7.88 (d, 1H, ArH), 7.75 (d, 1H, ArH), 7.43 (s, 1H, ArH), 4.33 (s, 2H, CH ₂), 3.12 (s, 3H, OCH ₃), 3.63 (s, 3H, OCH ₃) MS: <i>m/z</i> (%) 248.08 (M + 68%), 240.11 (100%), 163.45 (36%) 8.0 (s, 1H, NH), 8.12 (s, 1H, ArH), 7.98 (d, 1H, ArH), 7.66 (d, 1H, ArH), 4.55 (s, 2H, CH ₂), 3.42 (s, 3H, OCH ₃) MS: <i>m/z</i> (%) 263.05 (M + 65%), 201.17 (100%), 170.80 (35%) 8.0 (s, 1H, NH), 7.40 (s, 2H, ArH), 4.30 (s, 2H, CH ₂), 3.10 (s, 3H, OCH ₃), 2.34 (s, 3H, for two CH ₃) MS: <i>m/z</i> (%) 246.26 (M + 100%), 145.17 (86%), 104.16 (27%)	62.60/62.52	5.21/5.17	12.06/11.96
4g	C ₁₂ H ₁₂ N ₂ O ₄	248.08	182–85	87	3202, 1728, 1677		58.06/57.98	4.87/4.79	11.29/11.19
4h	C ₁₁ H ₉ N ₃ O ₅	263.05	202–05	83	3228, 1735, 1698		50.20/50.13	3.45/3.34	15.96/15.89
4i	C ₁₃ H ₁₄ N ₂ O ₃	246.26	215–17	88	3185, 1720, 1670		63.40/63.31	5.73/5.69	11.38/11.33

^a All the melting points (M.P.) were found to be identical to the authentic samples prepared according to the procedure reported in the literature [22].
M.W.: Molecular Weight; cald./exp.: calculated/experimental.



SCHEME 1: Schematic presentation of the synthesis of the compounds.

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