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Efficient Synthesis of 3-Hydroxy-1,4-benzodiazepines Oxazepam and Lorazepam by New Acetoxylation Reaction of 3-Position of 1,4-Benzodiazepine Ring

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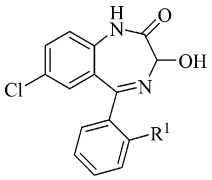
Abstract:

Simple, efficient, and scalable syntheses of 3-hydroxy-1,4-benzodiazepines, oxazepam (1), and lorazepam (2) were developed. The syntheses are based on the new acetoxylation reaction of the 3-position of the 1,4-benzodiazepine ring. The reaction involves iodine (20−50 mol %)-catalyzed acetoxylation in the presence of potassium acetate (2 equiv) and potassium peroxydisulfate (1−2 equiv) as a stoichiometric oxidant affording the corresponding 3-acetoxy-1,4-benzodiazepines in good-to-high yields. The latter were converted by selective saponification to 3-hydroxy-1,4-benzodiazepines of very high purity (>99.8%) in an overall yield of 83% (oxazepam) and 64% (lorazepam).

Introduction

From the class of 3-hydroxy-1,4-benzodiazepines, oxazepam (**1**) and lorazepam (**2**) are very important pharmaceutically active substances widely used for the treatment of anxiety.[1]



1: R^1 = H
2: R^1 = Cl

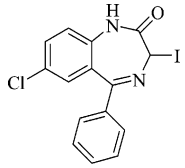
Although these drugs are more than 30 years old now, they are still within most prescribed anxiolytic drugs. Also the current prices for these two products as pharmaceutically active substances (APIs), oxazepam (100−150 USD/kg) and lorazepam (300−400 USD/kg), suggest that they are more expensive than one could expect for such old drugs. One of the reasons for this situation is in the employed technology which includes a well-known route to 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**) or 7-chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (**4**), followed by conversion to 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4*N*-oxide (**5**) and 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4*N*-oxide (**6**). Compound **5** or **6** is subjected to the Polonovsky rearrangement to give the 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7**) or 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**8**).[2] Finally oxazepam (**1**) or lorazepam (**2**) are produced by controlled saponification by various methods (Scheme 1).

Our company has a long tradition in the production of 1,4-benzodiazepines, and a lot of work has been carried out to simplify the overall process to oxazepam and lorazepam. Here we report about our recent results which allow us to produce these products by a significantly simplified, efficient, and cost-effective route.

Results and Discussion

Starting 1,4-benzodiazepines **3** and **4** were prepared from 2-amino-5-chloro-benzophenone (**9**) or 2-amino-5,2′-dichlorobenzophenone (**10**)[3] by reaction with chloroacetyl chloride affording 2-chloroacetamido-5-chlorobenzophenone (**11**) and 2-chloroacetamido-5,2′-dichlorobenzophenone (**12**). The latter were converted to 1,4-benzodiazepines **3** and **4** by modification of the known hexamethylenetetramine-(HMTM)-based cyclization reaction developed by Blažević and Kajfež (Scheme 2).[4]

The synthesis of 3-acetoxy-1,4-benzodiazepines **7** and **8** by direct acetoxylation of 1,4-benzodiazepines **3** and **4** with lead(IV) acetate and potassium iodide in acetic acid is known from the literature.[5] Despite the fact that this process proceeds cleanly and effectively, the use of lead-containing reagent is completely unacceptable for industrial production of APIs. However from the observation of this reaction we concluded that the process presumably includes the iodination of the 1,4-benzodiazepine ring followed by substitution of 3-iodo-7-chloro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**13**) with acetic acid (solvent) to give the 3-acetoxy derivative **7**.



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To check this prediction we have probed the reaction of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-

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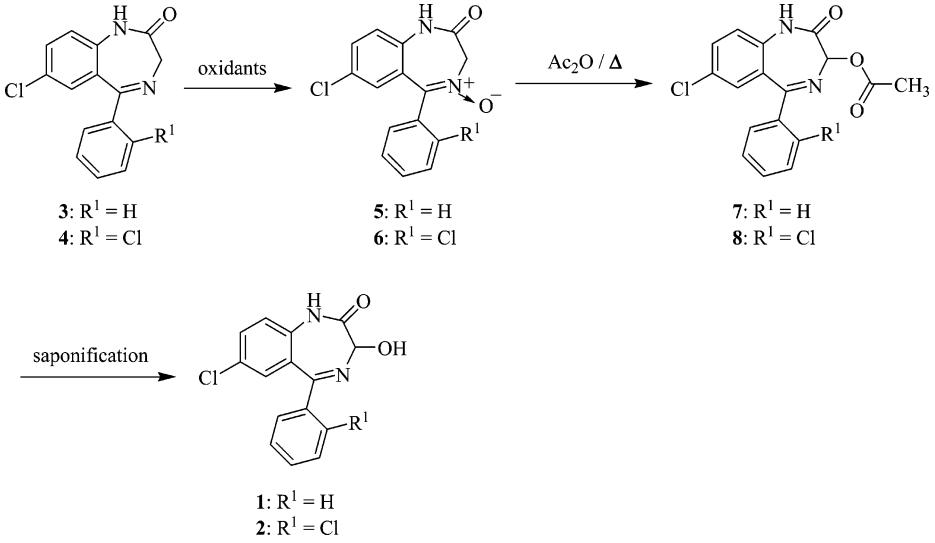
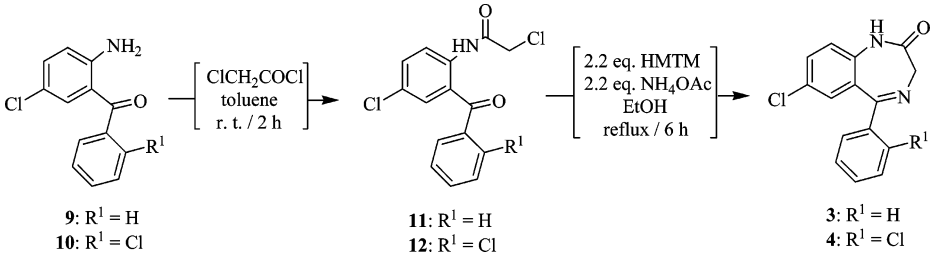
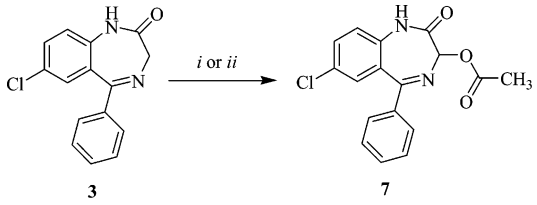
Scheme 1. **Common synthetic route to oxazepam (1) and lorazepam (2)**



Scheme 2. **Synthesis of 1,4-benzodiazepines 3 and 4**



Scheme 3. **Direct acetoxylation of 1,4-benzodiazepine 3**



i = 1.1 eq. KI / 2 eq. $Cu(OAc)_2$ / 2 eq. KOAc / HOAc / 80 °C / 5 h; 73%
ii = 1 eq. I_2 / 2 eq. $(NH_4)_2S_2O_8$ / 2 eq. KOAc / HOAc / 80 °C / 6 h; 84%

one (**3**) with an alternative iodide-oxidant, copper(II) acetate (2 equiv), in the presence of potassium iodide (1.1 equiv) and potassium acetate (2 equiv) in glacial acetic acid where expected 3-acetoxy-1,4-benzodiazepine **7** was obtained in 73% yield, indeed (Scheme 3). This indicates that this conversion also involves the combined iodination reaction and subsequent substitution of transient iodo-intermediate **13** with acetic acid or acetate ion to furnish 3-acetoxy derivative **7**.

As all iodination reactions are actually reversible, the suitable iodide-removing agent must be present.[6] The iodides can be eliminated from an equilibrium by oxidation (back to iodine).[7] Some metallic salts which have been employed as iodination reagents act as both oxidant and precipitation reagents for iodide ions (CuI, AgI, TlI).[8] Herein copper(II) acetate acts as both stoichiometric oxidant and precipitation reagent. The same system has been successfully used for the iodination of electron-rich arenes.[9]

Furthermore we tried to use the combination of iodine and a stoichiometric oxidant. First we used ammonium peroxydisulfate ($(NH_4)_2S_2O_8$; 2 equiv) in connection with iodine (1 equiv) where the expected 3-acetoxy-derivative **7** was also isolated in 84% yield (Scheme 3).

Moreover this reaction can be carried out catalytically (Scheme 4). To our pleasant surprise several possible reagents efficiently act as stoichiometric oxidants (2 equiv) in the model iodine-(50 mol %)-catalysed acetoxylation of 1,4-benzodiazepines **3** and **4** in the presence of potassium acetate (2 equiv) in glacial acetic acid at elevated temperatures (65−90 °C). Among them, various oxidants capable of oxidizing iodide to iodine were effective: manganese dioxide, potassium ($K_2S_2O_8$) and ammonium peroxydisulfate, calcium hypochlorite, nitrous acid ($NaNO_2$/HOAc), and

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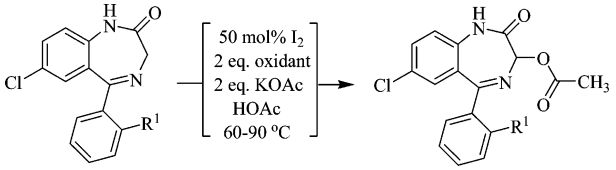
Scheme 4. **Iodine-catalysed acetoxylation of 1,4-benzodiazepines 3 and 4 in glacial acetic acid in the presence of various stoichiometric oxidants**



3: R^1 = H
4: R^1 = Cl

7: R^1 = H
8: R^1 = Cl

Table 1. **Influence of various stoichiometric oxidants on the iodine-catalysed acetoxylation of 1,4-benzodiazepines 3 and 4 to 3-acetoxy derivatives 7 and 8 (Scheme 4)**

run	reactant	product	oxidant	temp (°C)	time[a] (h)	yield[b] (%)
1	**3**	**7**	MnO_2	90	2.5	61
2	**3**	**7**	$NaNO_2$	90	1	66
3	**3**	**7**	$Ca(OCl)_2$	70	1.5	80
4	**3**	**7**	$(H_2N)_2COH_2O_2$	65	1	72
5	**3**	**7**	$NaBO_34H_2O$	90	2.5	71
6	**3**	**7**	$Na_2CO_31.5H_2O_2$	70	2.5	63
7	**3**	**7**	$(NH_4)_2S_2O_8$	70	3	84
8	**3**	**7**	$K_2S_2O_8$	70	3	86
9	**4**	**8**	MnO_2	90	2	65
10	**4**	**8**	$NaNO_2$	90	1	74
11	**4**	**8**	$Ca(OCl)_2$	70	1.5	75
12	**4**	**8**	$(H_2N)_2COH_2O_2$	70	1	73
13	**4**	**8**	$NaBO_3H_2O_2$	90	2	72
14	**4**	**8**	$K_2S_2O_8$	70	3	79

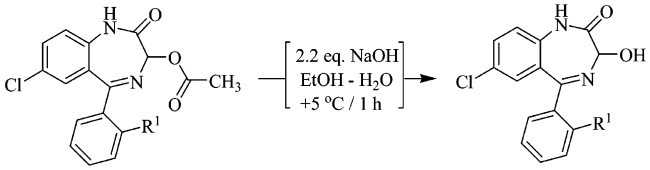
[a] Determined by TLC analysis. [b] Yields of pure products isolated by preparative chromatography.

peroxide-based oxidants such as $Na_2CO_3 \cdot 1.5H_2O_2$, $(H_2N)_2CO \cdot H_2O_2$, and $NaBO_3 \cdot 4H_2O$.[10]

In all cases, 3-acetoxy derivatives **7** and **8** were isolated after purification by column chromatography in good-to-high yields (Table 1).

From this study $K_2S_2O_8$ was selected as the most suitable due to its efficacy, availability, and low price. The optimal reaction temperature for $K_2S_2O_8$-mediated reactions is between 65 and 70 °C. To reach the highest conversion and yields, in both cases the reaction times were extended to 8−10 h (optimal) in order to avoid the contamination of final products **7** and **8** with traces of starting compounds **3** and **4**. The latter can cause significant difficulties during the purification procedures since the final 3-acetoxy derivatives **7** and **8** have to be of very high purities (>99.7%) in order to produce high-quality oxazepam (**1**) or lorazepam (**2**) active substances. In addition, it was found that employed amounts of both iodine catalyst (to 20−40 mol %) and potassium peroxydisulfate (to 0.8−1 equiv) can be reduced without a significant decrease in either conversion or reaction yield. Lower amounts of iodine catalyst (5 or 10 mol %) led to incomplete conversions (80−90%).

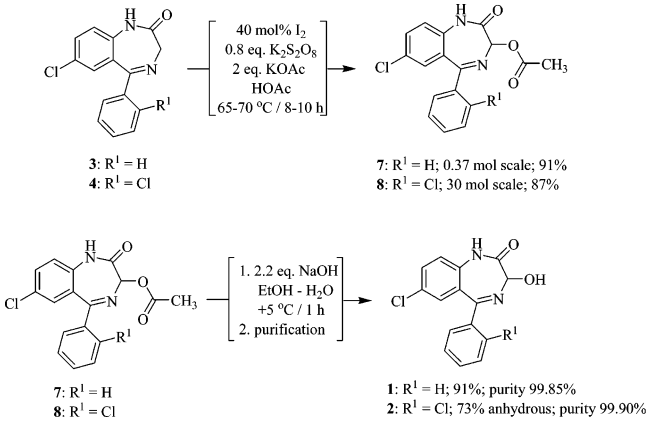
Scheme 5. **Preparation of oxazepam (1) and lorazepam (2)**



7: R^1 = H
8: R^1 = Cl

1: R^1 = H
2: R^1 = Cl

Scheme 6. **New syntheses of oxazepam (1) and lorazepam (2) on a larger scale**



3: R^1 = H
4: R^1 = Cl

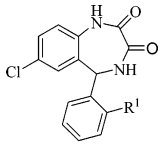
7: R^1 = H; 0.37 mol scale; 91%
8: R^1 = Cl; 30 mol scale; 87%

7: R^1 = H
8: R^1 = Cl

1: R^1 = H; 91%; purity 99.85%
2: R^1 = Cl; 73% anhydrous; purity 99.90%

Thus obtained 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7**) and 3-acetoxy-7-chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (**8**) were converted to oxazepam (**1**) and lorazepam (**2**) by controlled saponification with sodium hydroxide in an ethanol−water mixture in >90% yields (Scheme 5).

These procedures have been proved to give the products of high purity and minimal amounts of unwanted 7-chloro-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepin-2,3(1*H*)-dione (**14**) and 7-chloro-5-(2-chlorophenyl)-4,5-dihydro-2*H*-1,4-benzodiazepin-2,3(1*H*)-dione (**15**) known as base-catalysed rearrangement products of 3-hydroxy-1,4-benzodiazepines.[11]



14: R^1 = H
15: R^1 = Cl

Crude oxazepam (**1**) was purified with toluene to give the final product of pharmaceutical-grade purity (99.85%).[12] In contrast, crude lorazepam (actually lorazepam-hydrate) was first converted to a lorazepam-ethanol solvate[13] with ethanol and then desolvated with toluene to give a pharmaceutically pure anhydrous substance (99.90%).[14]

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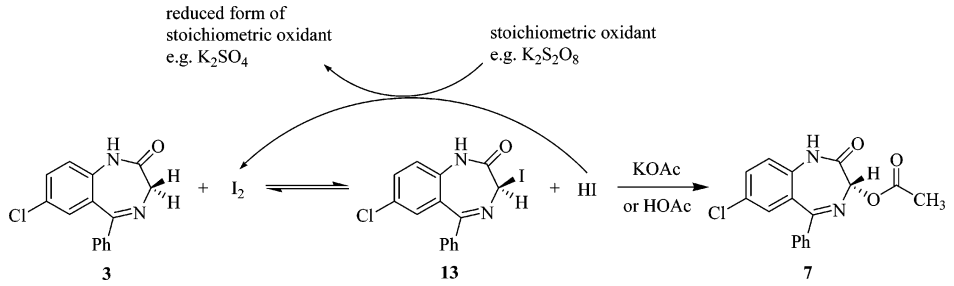
Scheme 7. **Plausible mechanism of iodine-catalysed acetoxylation of 1,4-benzodiazepine 3 in the presence of KOAc/HOAc and a stoichiometric oxidant**



After a number of succesfully repeated batches at higher scales (20−100 g), thus described synthesis of lorazepam (**2**) was scaled-up in the pilot plant to 1-kg scale (Scheme 6). The main points which arose from the pilot-scale examination are the following:

1. The acetoxylation reaction is somewhat exothermic, but the reaction can be successfully controlled by stepwise addition of $K_2S_2O_8$.

2. High reproducibilities concerning conversions, yields, and impurity profiles were observed in both the acetoxylation reaction and the subsequent saponification reaction.

At the same time synthesis of oxazepam (**1**) was tested on the 100-g scale (Scheme 6).

We have performed a few experiments in order to clarify some mechanistic points of this new iodine-catalysed acetoxylation reaction. According to our plausible mechanism this reaction proceeds by iodination of the 3-position of the 1,4-benzodiazepine ring with iodine which is accompanied by evolution of hydroiodic acid (iodide ion). Thus formed 7-chloro-3-iodo-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**13**) is subjected to a rapid substitution reaction with acetate or acetic acid to form 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7**). The stoichiometric oxidant oxidizes the liberated hydroiodic acid (iodide ion) back to the iodine, thus closing a catalytic cycle (Scheme 7). All attempts to isolate iodo-derivative **13** were unsuccessful. We have tried to prepare **13** separately from 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**) by well-known iodination methods which include very mild conditions, but only an extensive decomposition was observed.[6]

Conclusion

We have developed a new synthesis of 3-acetoxy-1,4-benzodiazepines by a direct acetoxylation reaction of the 3-position of the 1,4-benzodiazepine ring. The reaction is catalyzed by iodine (20−50 mol %) in the presence of potassium peroxydisulfate as a stoichiometric oxidant (0.8−2 equiv) and potassium acetate (2 equiv) in acetic acid as solvent at elevated temperatures (65−90 °C). This reaction was employed in the new syntheses of widely used anxiolytic drugs oxazepam (**1**) and lorazepam (**2**). The processes for lorazepam (**2**) were scaled-up giving a high reliable, efficient, and cost-effective approach for commercial production.

Experimental Section

IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer, and wave numbers, ν, were expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a AV Bruker (600 MHz) spectrometer, and shifts, δ, are given in ppm downfield from TMS as an internal standard. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien with Kieselgel $60F_{254}$. HPLC analyses were carried out on a Thermo Separation Products Instruments (San Jose, CA) HPLC system comprising a vacuum degasser (SCM 1000), quaternary gradient pump (P 4000), an autosampler (AS 3000), and a diode array UV−vis detector (UV 3000HR). The detector output was stored and reprocessed using a ChromQuest 2.51 software package. HPLC method for oxazepam (**1**) and its intermediates **9**, **11**, **3**, and **7**: λ = 230 nm; Phenomenex Synergie Hydro-RP column (150 mm × 4.6 mm; 4 μm); Linear gradient method: 0−27 min MeOH/buffer solution* (55:45, v/v), 27−40 min (75:25, v/v) as mobile phase; t_R (**1**) 10.40 min, t_R (**9**) 35.13 min, t_R (**11**) 36.08 min, t_R (**3**) 17.24 min, t_R (**7**) 19.57 min; flow 1 mL/min. Method for lorazepam (**2**) and its intermediates **10**, **12**, **4**, and **8**: λ = 235 nm; Phenomenex Synergie Polar-RP column (150 mm × 4.6 mm; 4 μm); Linear gradient method: 0−18 min MeOH/buffer solution* (62:38, v/v), 18−30 min [MeOH/buffer solution* (62:38, v/v)]/MeCN (50:50, v/v) as mobile phase; t_R (**2**) 7.17 min, t_R (**10**) 17.68 min, t_R (**12**) 27.39 min, t_R (**4**) 9.72 min, t_R (**8**) 11.82 min; flow 1 mL/min. *Buffer solution: KH_2PO_4 (1.70 g) was dissolved in 450 mL of HPLC-grade water. pH was corrected to 3 with H_3PO_4 (85%). Then triethylamine (1.8 mL) and water to 500 mL were added. Melting points were determined using a Büchi B-540 instrument. Elemental analyses were performed by the Central Analytical Service at Ruđer Bošković Institute.

Preparation of 2-Chloroacetamido-5-chlorobenzophenone (11) and 2-Chloroacetamido-5,2′-dichlorobenzophenone (12). General Procedure. To a solution of 2-amino-5-chlorobenzophenone (**9**; 23.17 g, 0.1 mol) or 2-amino-2′,5-dichlorobenzophenone (**10**; 26.61 g, 0.1 mol) in toluene (200 mL) a solution of chloroacetyl chloride (8.4 mL, 11.93 g, 0.106 mol, 1.06 equiv) in toluene (20 mL) was added dropwise at +10 °C during 0.5 h. The reaction mixture was stirred at room temperature for 3 h. The resulting reaction mixture was evaporated to dryness. The crude product was purified by stirring with 96% ethanol (100 mL) at room temperature for 20 h. The crystals were separated by filtration, washed with 96% ethanol (3 × 10 mL), and dried in a high vacuum at 50 °C for 20 h.

2-Chloroacetamido-5-chlorobenzophenone (11): 29.98 g (97.3%) of colorless crystals, mp 119.5−121.0 °C. R_f (CH_2-

Cl_2) 0.55. IR (KBr) ν 3278, 3105, 3058, 2943, 1686, 1641, 1596, 1579, 1518, 1446, 1394, 1323, 1290, 1256, 1231 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 4.16 (s, CH_2Cl), 7.44−7.49 (m, 4H), 7.56−7.64 (m, 1H), 7.67−7.70 (m, 2H), 8.54 (d, 1H, arom., J = 9.3 Hz), 11.42 (s, 1H, N*H*) ppm. ^{13}C NMR (600 MHz, $CDCl_3$) δ 42.74, 122.56, 125.01, 127.85, 128.19, 129.63, 132.23, 132.72, 133.35, 137.12, 137.28, 164.92, 197.26 ppm.

2-Chloroacetamido-5,2′-dichlorobenzophenone (12): 33.61 g (98.1%) of colorless crystals, mp 160.2−162.0 °C. R_f (CH_2Cl_2) 0.63. IR (KBr) ν 3183, 3007, 1690, 1645, 1600, 1578, 1510, 1434, 1396, 1315, 1288, 1269, 1241 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 4.25 (s, 2H, CH_2Cl), 7.35−7.45 (m, 3H), 7.48−7.75 (m, 3H), 8.77 (d, 1H, arom., J = 9.1 Hz), 12.18 (s, 1H, N*H*) ppm. ^{13}C NMR (600 MHz, $CDCl_3$) δ 43.00, 122.12, 126.81, 128.25, 128.71, 130.12, 130.84, 131.65, 133.25, 135.19, 137.51, 138.65, 165.60, 197.64 ppm.

Preparation of 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (3) and 7-Chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (4). General Procedure. To a solution of 2-chloroacetamido-5-chlorobenzophenone (**11**; 24.65 g, 0.08 mol) or 2-chloroacetamido-2′,5-dichlorobenzophenone (**12**; 27.41 g, 0.08 mol) in 96% ethanol (500 mL) hexamethylenetetramine (HMTM; 24.65 g, 0.18 mol, 2.2 equiv) and ammonium acetate (13.57 g, 0.18 mol, 2.2 equiv) were added. The reaction mixture was stirred at reflux temperature for 6 h. Then the reaction mixture was evaporated to dryness. Distilled water (300 mL) was added, and the resulting suspension was stirred at 60 °C for 0.5 h. The suspension was cooled to +15 °C and filtered. A crude product was dried at 105 °C for 5 h. The crude product was purified with toluene (80 mL) at 70 °C for 0.5 h. The obtained suspension was cooled to +10 °C and filtered, and the crystals were washed with cold toluene (3 × 10 mL). The purified products were dried at 105 °C for 5 h.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (3): 16.50 g (76.2%) of colorless crystals, mp 217.3−218.1 °C. R_f (CH_2Cl_2/2-PrOH, 9.5:0.5) 0.36. IR (KBr) ν 3177, 3041, 2956, 2845, 1681, 1606, 1575, 1479, 1444, 1384, 1360, 1321, 1304, 1285, 1259, 1234, 1194 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 4.33 (s, 2H, COCH_2N), 7.18 (d, 1H, arom., J = 8.7 Hz), 7.26−7.29 (m, 1H), 7.37−7.46 (m, 5H), 7.51−7.54 (m, 1H), 10.14 (s, 1H, N*H*) ppm. ^{13}C NMR (600 MHz, DMSO-d_6) δ 56.48, 122.75, 128.34, 128.44, 128.72, 129.56, 129.68, 130.60, 131.80, 137.45, 138.75, 169.95, 172.25 ppm.

7-Chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (4): 21.12 g (86.5%) of colourless crystals, mp 197.5−200.0 °C. R_f (CH_2Cl_2/2-PrOH, 9.5:0.5) 0.40. IR (KBr) ν 3344, 3213, 3118, 3063, 2961, 1684, 1618, 1593, 1572, 1485, 1444, 1434, 1390, 1366, 1324, 1296, 1255, 1235 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 4.39 (s, 2H, COCH_2N), 7.03 (d, 1H, arom., J = 2.2 Hz), 7.13−7.16 (m, 1H), 7.19−7.52 (m, 5H), 10.31 (s, 1H, N*H*) ppm. ^{13}C NMR (600 MHz, DMSO-d_6) δ 56.34, 122.51, 126.81, 128.88, 129.94, 130.82, 131.75, 132.94, 136.55, 138.06, 169.26, 171.33 ppm.

Preparation of 3-Acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7) by Copper(II) Acetate/Potassium Iodide-Mediated Acetoxylation. To a solution of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**; 2.71 g, 0.01 mol) in glacial acetic acid (30 mL) copper(II) acetate monohydrate (3.99 g, 0.02 mol, 2 equiv), potassium iodide (1.83 g, 0.011 mol, 1.1 equiv), and potassium acetate (1.96 g, 0.02 mol, 2 equiv) were added. The resulting reaction mixture was heated at 80 °C for 5 h. The reaction mixture was evaporated under a reduced pressure to dryness. The residue was extracted with chloroform (5 × 30 mL) and filtered to remove inorganic solids. Combined organic extracts were washed with a 10% aqueous solution of $Na_2S_2O_3 \cdot 5H_2O$ (2 × 30 mL) and water (2 × 30 mL) and evaporated to dryness. The crude product (R_f 0.45) was purified by preparative chromatography on a silica gel column (200 g) with dichloromethane/2-propanol (9.5:0.5) as an eluent to yield 2.40 g (73.0%) of pure **7** as colorless crystals, mp 240−242 °C.

IR (KBr) ν 3408, 3230, 3153, 3045, 2926, 1925, 1750, 1720, 1608, 1578, 1483, 1446, 1423, 1390, 1331, 1316, 1261, 1232, 1169 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3COO), 5.96 (s, 1H, C*H*OAc), 7.24−7.59 (m, 8H), 9.99 (s, 1H, N*H*) ppm. ^{13}C NMR (600 MHz, $CDCl_3$) δ 21.04, 84.39, 123.36, 128.32, 129.39, 129.80, 130.19, 131.07, 132.45, 136.02, 137.28, 165.93, 167.03, 170.24 ppm.

Preparation of 3-Acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7) and 3-Acetoxy-7-chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (8) by Iodine-Catalysed Acetoxylation with Various Stoichiometric Oxidants. To a solution of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**; 2.71 g, 0.01 mol) or 7-chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (**4**; 3.05 g, 0.01 mol) in glacial acetic acid (50 mL) potassium acetate (1.96 g, 0.02 mol, 2 equiv.), iodine (1.27 g, 5 mmol, 50 mol %), and one of the following stoichiometric oxidants (0.02 mol, 2 equiv), MnO_2 (1.74 g; at once), $NaNO_2$ (1.38 g; during 5 min), $Ca(OCl)_2$ (2.86 g; during 5 min), $(H_2N)_2CO \cdot H_2O_2$ (1.88 g; at once), $NaBO_3 \cdot 4H_2O$ (3.08 g; at once), $Na_2CO_3 \cdot 1.5H_2O_2$ (3.14 g; during 5 min), $(NH_4)_2S_2O_8$ (4.56 g; at once), or $K_2S_2O_8$ (5.41 g; at once), were added. The reaction mixture was stirred at 65−90 °C during the time indicated in Table 1. Then the volatiles were evaporated under a reduced pressure. The residue was extracted with boiling chloroform (3 × 50 mL) and filtered to remove inorganic solids. The combined organic extracts were washed with a 10% aqueous solution of $Na_2S_2O_3 \cdot 5H_2O$ (2 × 50 mL) and distilled water (2 × 30 mL) and dried (Na_2SO_4), filtered, and evaporated to dryness. The crude product **7** or **8** was purified by preparative chromatography on a silica gel (200 g) column using dichloromethane/2-propanol (9.5:0.5) as an eluent. The isolated products **7** (R_f 0.45) or **8** (R_f 0.45) in all experiments gave the same IR, ^1H NMR, and ^{13}C NMR spectra.

3-Acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7): IR, ^1H NMR, and ^{13}C NMR spectra correspond to the spectra of the product **7** obtained by Cu(OAc)$_2$/KI-mediated acetoxylation.

3-Acetoxy-7-chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (8): Colourless crystals, mp 257.5−259.7 °C. IR (KBr) ν 3401, 3332, 3161, 3085, 3068, 2930, 1925, 1708, 1630, 1600, 1592, 1570, 1482, 1460, 1439, 1391, 1367, 1325, 1246 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 2.33 (s, 3H, CH_3COO), 6.02 (s, 1H, C*H*OAc), 7.08−7.60 (m, 7H), 9.79 (s, 1H, N*H*) ppm. ^{13}C NMR (600 MHz, DMSO-d_6) δ 20.99, 84.02, 123.19, 126.95, 128.70, 129.07, 129.80, 130.05, 131.16, 131.33, 132.60, 133.08, 135.25, 136.97, 165.67, 166.27, 170.16 ppm.

Preparation of 3-Acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7) by Optimized Iodine-Catalysed Acetoxylation. To a solution of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**; 100.00 g, 0.37 mol) in glacial acetic acid (1000 mL) potassium acetate (72.62 g, 0.74 mol, 2 equiv) and iodine (37.56 g, 0.148 mol, 40 mol %) were added. The reaction mixture was heated to 65 °C with stirring. Then the potassium peroxydisulfate (80.00 g, 0.296 mol, 0.8 equiv) was added in several portions during 4 h. The reaction mixture was stirred at 65−70 °C for an additional 4 h. The reaction mixture was evaporated under a reduced pressure. Then a solution of sodium thiosulfate pentahydrate (75 g) in distilled water (2000 mL) was added. The thus obtained suspension was heated to 70 °C with stirring and maintained at this temperature for 2 h. The suspension was cooled to +10 °C, filtered, washed with hot distilled water (3 × 100 mL), and dried at 105 °C for 20 h.

The crude product **7** (120 g) was dissolved in hot (70−80 °C) *N*,*N*-dimethylformamide (360 mL) and filtered to remove traces of insoluble materials. To the clear DMF solution of **7**, 2-propanol (360 mL) was added dropwise with stirring at 70 °C during 0.5 h. The thus obtained suspension was stirred at this temperature for an additional 1 h and then cooled to +10 °C during 1 h. The crystals were separated by filtration, washed with 2-propanol (3 × 20 mL), and dried in a high vacuum at 80 °C during 5 h. The same recrystallization procedure was repeated to yield 111.01 g (91.3%) of 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7**) as colourless crystals, mp 235.0−237.9 °C. Purity: >99.8 by HPLC. IR, ^1H NMR, and ^{13}C NMR spectra of the product correspond to the spectra of the product obtained in $Cu(OAc)_2$/KI-mediated acetoxylation.

Preparation of Oxazepam (1). To a stirred solution of 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7**; 100.00 g, 0.304 mol) in 96% ethanol (1000 mL), cooled to +5 °C, a solution of sodium hydroxide (26.78 g, 0.67 mol, 2.2 equiv) in distilled water (600 mL) was added dropwise during 0.5 h. The reaction mixture was stirred at +5 °C for an additional 1 h. Then glacial acetic acid (40 mL) was added dropwise during 15 min. The mixture was cooled to +10 °C, and crystals were separated by filtration, washed with distilled water (3 × 100 mL), and dried in a high vacuum at 80 °C for 5 h. Thus obtained crude oxazepam (**1**) was purified with boiling 96% ethanol (800 mL) during 1 h. The suspension was cooled to +10 °C. Crystals were filtered, washed with cold 96% ethanol (3 × 30 mL), and dried in a high vacuum at 80 °C during 5 h to yield 79.75 g (91.4%) of pure oxazepam (**1**) as white crystals, mp 200.0−204.1 °C. Purity: 99.85% by HPLC. R_f (CH_2Cl_2/2-PrOH, 9:1) 0.50. IR (KBr) ν 3341, 3140, 2945, 2852, 1713, 1692, 1599, 1563, 1478, 1445, 1387, 1354, 1326, 1290, 1259, 1219 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 4.76 (d, 1H, J = 8.6 Hz), 6.39 (d, 1H, J = 8.6 Hz), 7.16−7.18 (m, 1H), 7.23−7.27 (m, 1H), 7.38−7.43 (m, 5H), 7.58−7.62 (m, 1H), 10.81 (s, 1H, N*H*) ppm. ^{13}C NMR (600 MHz, DMSO-d_6) δ 80.30, 120.64, 124.07, 125.26, 125.84, 126.71, 127.93, 129.24, 135.19, 135.44, 159.78, 167.25 ppm. Anal. Calcd for $C_{15}H_{11}N_2OCl$: C, 66.55; H, 4.10; N, 10.35; Cl, 13.10. Found: C, 66.46; H, 4.06; N, 10.31; Cl, 13.05.

Preparation of 3-Acetoxy-7-chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (8). To a suspension of 7-chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (**4**; 9.30 kg, 30.48 mol) in acetic acid (93 L) potassium acetate (5.98 kg, 60.96 mol, 2 equiv) and iodine (3.09 kg, 12.19 mol, 40 mol %) were added. The resulting suspension was heated to 65 °C during 0.5 h until all solid materials have been dissolved. After that the first portion of potassium peroxydisulfate (1.10 kg) was added by keeping the temperature at about 65 °C. Another five portions of oxidant were added sequentially after every 1 h (the overall amount of $K_2S_2O_8$ is 6.60 kg, 24.38 mol, 0.8 equiv) while the temperature was maintained between 65 and 70 °C with external water cooling. The reaction mixture was heated at 65−70 °C for 5 h further. After that the solvent was distilled off under a reduced pressure (15 mbar), and to the residue demineralized water (100 L) was added. The suspension was stirred at room temperature for 12 h. Then a solution of $Na_2S_2O_3 \cdot 5H_2O$ (6.05 kg, 24.38 mol) in demineralized water (65 L) was added. After an additional 3 h of stirring the product was filtered off, washed with demineralized water (3 × 40 L), and dried under a vacuum at 80 °C for 15 h. The crude product (11 kg) was charged in three portions to the preheated *N*,*N*-dimethylformamide (35 L) at 80 °C. After all solid material was dissolved to give a dark brown solution, 2-propanol (35 L) was added dropwise during 15 min. The thus obtained suspension was cooled to +5 °C, stirred for 24 h, and filtered. The filter cake was washed with cold 2-propanol (3 × 8.5 L) and dried under vacuum at 85 °C for 20 h to give **8** (8.58 kg, 78%) as pale orange crystals. The purified product was than dissolved in *N*,*N*-dimethylformamide (26 L) preheated at 80 °C, and to the resulting solution 2-propanol (26 L) was added dropwise during 15 min. The suspension was cooled to +5 °C, stirred for 24 h, and filtered. The filter cake was washed with cold 2-propanol (3 × 6.5 L) and dried under vacuum at 85 °C for 20 h to give **8** (7.50 kg, 87.4%) as white crystals, mp 257.2−259.8 °C. Purity: >99.7% by HPLC.

Preparation of Lorazepam (2). To a well stirred suspension of 3-acetoxy-7-chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (**8**; 1.45 kg, 4 mol) in a mixture of 96% ethanol (20 L) and demineralized water (6.7 L) cooled to +5 °C, sodium hydroxide (0.27 kg, 6.8 mol, 1.7 equiv) dissolved in demineralized water (6.7 L) was added dropwise during 30 min. After stirring at +5 °C for 1 h further, to the resulting thick suspension a mixture of acetic

acid (1.17 L, 1.23 kg, 20.4 mol, 3 equiv) and demineralized water (1.17 L) was added dropwise during 15 min followed by an additional amount of demineralized water (6.7 L). After 1.5 h of stirring the product was filtered off, washed with demineralized water (5 × 4 L), and dried under a vacuum at 80 °C for 20 h to furnish lorazepam hydrate (**2a**; 1.21 kg, 94.5%) as colourless crystals.

The crude lorazepam hydrate (**2a**; 1.21 kg) was suspended in ethanol (8.5 L), refluxed for 0.5 h, cooled to +10 °C, and stirred at this temperature for an additional 1 h. After filtration, the filter cake was washed with cold 96% ethanol (3 × 1.8 L), and dried in a high vacuum at 40 °C for 12 h to give lorazepam−ethanol solvate (**2b**; 1.05 kg, 86.8%) as white crystals.

The resulting lorazepam−ethanol solvate (**2b**; 1.05 kg) was charged in toluene (7.4 L) preheated at 80 °C, and stirring was continued for 30 min. After cooling to +10 °C the resulting suspension was stirred for an additional 1.5 h. The product was filtered off, washed with cold toluene (3 × 1.9 L), and dried under a vacuum at 50 °C for 24 h to yield pure anhydrous lorazepam (**2**; 0.94 kg, 89.5%) as white crystals. Purity: 99.90% by HPLC.

Lorazepam (2): White crystals, mp 182.0−183.0 °C. R_f (CH_2Cl_2/2-PrOH, 9:1) 0.57. IR (KBr) ν 3363, 1704, 1687, 1618, 1478, 1436, 1387, 1323, 1259, 1234 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 4.82 (d, 1H, J = 8.6 Hz), 6.44 (d, 1H, J = 8.6 Hz), 6.90−6.91 (m, 1H), 7.21−7.24 (m, 1H), 7.44−7.46 (m, 1H), 7.47−7.60 (m, 4H), 10.94 (s, 1H, N*H*) ppm. ^{13}C NMR (600 MHz, DMSO-d_6) δ 82.98, 123.22, 126.94, 127.54, 127.78, 128.80, 129.85, 131.94, 137.23, 137.87, 162.10, 169.22 ppm. Anal. Calcd for $C_{15}H_{10}N_2OCl_2$: C, 59.04; H, 3.30; N, 9.18; Cl, 23.24. Found: C, 58.95; H, 3.26; N, 9.11; Cl, 23.21.

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