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New Efficient Synthesis of 1,4-Benzodiazepin-5-ones by Catalytic Aza-Wittig Reaction

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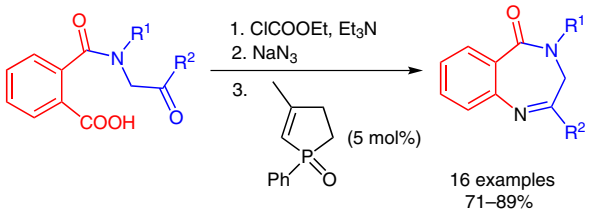

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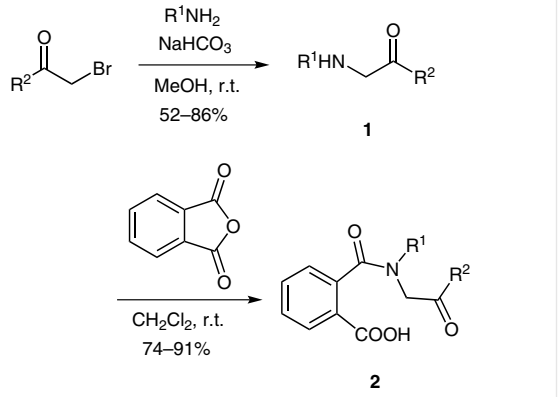
Abstract 1,4-Benzodiazepin-5-ones were synthesized in 71–89% yields from 2-isocyanato-*N*-(2-oxoalkyl)benzamides via a new catalytic intramolecular aza-Wittig reaction. Starting from easily accessible phthalic anhydride and α-arylamino ketones, the corresponding 2-{[(2-oxoalkyl)amino]carbonyl}benzoic acids underwent sequential formation of the acid azide and Curtis rearrangement to give 2-isocyanato-*N*-(2-oxoalkyl)benzamides that were reacted directly to give the final 2,4-diaryl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-ones and 4-aryl-2-*tert*-butyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-ones.

Key words 1,4-benzodiazepin-5-one, catalytic aza-Wittig reaction, Curtius reaction, acyl azide, isocyanate

Benzodiazepines are an important and widely used structural motif in many drugs and biologically active compounds, especially for the treatment of anxiety and sleep disorders.[1] A large number of derivatives of these heterocycles have also been found to show other biological activity. For example, some 1,4-benzodiazepin-5-ones were recently reported to exhibit significant anticancer,[2] HIV-1 reverse transcriptase inhibitive,[3] histone deacetylase inhibitive,[4] and vitamin D receptor transactivation inhibitive activity.[5] In addition, 1,4-benzodiazepin-5-one rings are also found as building blocks in some natural products such as anthramycin, chicamycin, and DC-81, which are produced from various *Streptomyces* bacteria.[6] Although much effort has been directed toward the construction of 1,4-benzodiazepines,[7] only few efficient synthesis methods for 1,4-benzodiazepin-5-ones have been developed over the past few decades.[8–11] For example, some 1,4-benzodiazepin-5-one derivatives were prepared either by intramolecular azide or nitrilimine cycloadditions,[8] or by palladium-catalyzed amination of *N*-allylanthranilamides.[9] Other 1,4-benzodiazepin-5-ones were also obtained from intramolecular aza-Wittig reactions by using stoichiometric phosphine as reactant.[10] Therefore, there is an unmet need for the development of a practical, general, and efficient pathway toward 1,4-benzodiazepin-5-ones starting from easily accessible materials.

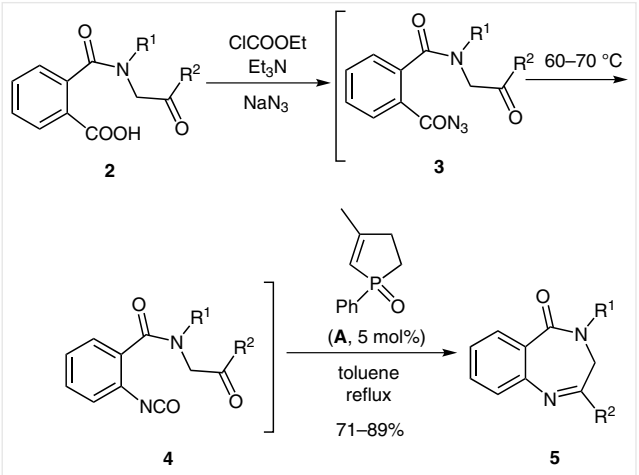
The aza-Wittig reaction of an iminophosphorane with a carbonyl compound provides an excellent method for the construction of the C=N bond under mild and neutral reaction conditions.[12] The intramolecular aza-Wittig reaction has become an efficient tool in the construction of various N-heterocycles through intramolecular cyclization with a wide variety of carbonyl groups.[13] However, the aza-Wittig reaction produces stoichiometric triphenylphosphine oxide as a byproduct, which results in low atom efficiency of the reaction, and, in some cases, the separation of the product from the byproduct triphenylphosphine oxide is problematic. In 2008, Marsden reported firstly a catalytic aza-Wittig reaction using carbonyl isocyanate derivatives that cyclize to produce benzoxazoles and phenanthridines, under catalysis by commercially available phospholene oxide.[14] In contrast to the conventional aza-Wittig reaction, the catalytic aza-Wittig process shows high atom efficiency (solely releasing CO_2 as a byproduct) by utilizing a catalytic amount of an organophosphorus reagent. However, despite the immense importance of this reaction there remains only one reported example. The catalytic Wittig and aza-Wittig reaction may also be carried out using a catalytic amount of phosphine in the presence of stoichiometric reductant, usually a suitable silane.[15,16] Recently, we have been interested in the synthesis of various heterocycles via the aza-Wittig reaction[17] or catalytic aza-Wittig reaction.[16b] Herein we wish to report a new efficient synthesis of 1,4-benzodiazepin-5-ones by the catalytic aza-Wittig reaction, starting from easily accessible phthalic anhydride and α-arylamino ketones.

The required carbonyl acid derivatives **2** were easily obtained according to standard protocols (Scheme 1).[18] At first various α-arylamino ketones **1** were obtained by the alkylation of primary amines with α-bromo ketones in methanol according to the literature report.[19] Only such compounds **1** where R^1 is an aryl group and R^2 is an aryl or *tert*-butyl group can be prepared. We attempt to prepare compounds **1** with other alkyl groups than *tert*-butyl on the R^2 position, or with R^1 group different from aryl groups, however, all attempts failed probably due to the limitations of the method. Only compounds **1** which precipitate directly from the solvent may be prepared, otherwise a complex mixture resulted. The obtained α-arylamino ketones **1** reacted further with phthalic anhydride at room temperature to provide carbonyl acid derivatives **2** in good yields.



Scheme 1 Preparation of acid derivatives **2**

The next objective was transforming carbonyl acid **2** by Curtius reaction into carbonyl isocyanate intermediate **4**, which was then used to prepare the 1,4-benzodiazepin-5-one via catalytic aza-Wittig reaction. When carbonyl acid **2** was treated with ethyl chloroformate/triethylamine followed by sodium azide in tetrahydrofuran, the acyl azide **3** was produced. The azide **3** was then transformed into carbonyl isocyanate intermediate **4** by heating in toluene. Further heating the isocyanate **4** in toluene with a catalytic amount of phospholene oxide **A** afforded a single product, which was isolated and verified to be 1,4-benzodiazepin-5-one **5** (Scheme 2). All the reactions were carried out smoothly to give the corresponding 1,4-benzodiazepin-5-ones **5** in toluene at reflux temperature, and satisfactory yields were obtained with various substituents on the reactants (Table 1). As the R^2 group is an aromatic substituent, good yields were obtained whenever the substituent on the phenyl ring is an electron-withdrawing (entries 8–11) or electron-donating group (entries 6 and 7). It is noteworthy that good yields were obtained even when R^2 is a sterically hindered *tert*-butyl group (entries 15 and 16). The R^1 group has no obvious effects on the reaction yield regardless of the substituents (Cl, F, Me, OMe, OEt) on the benzene ring. The reaction was unsuccessful when the catalyst was changed to triphenylphosphine oxide, probably due to its low reactivity.



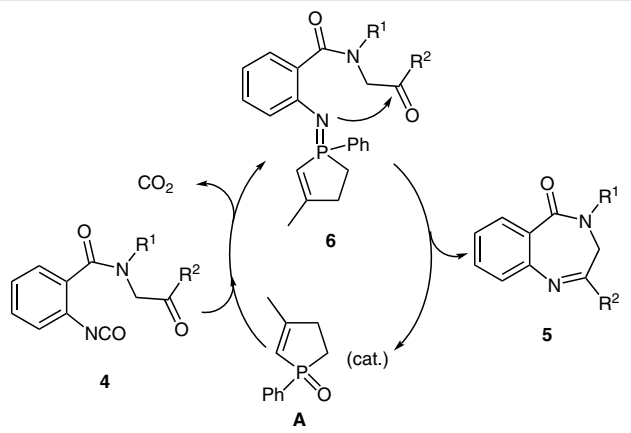
Scheme 2 Preparation of 1,4-benzodiazepin-5-ones **5**

Table 1 Preparation of 1,4-Benzodiazepin-5-ones **5**

Entry	Product	R^1	R^2	Yield[a] (%)
1	**5a**	4-MeC_6H_4	Ph	89
2	**5b**	Ph	Ph	87
3	**5c**	4-ClC_6H_4	Ph	75
4	**5d**	2-MeC_6H_4	Ph	71
5	**5e**	3-ClC_6H_4	Ph	72
6	**5f**	Ph	4-$MeOC_6H_4$	82
7	**5g**	4-MeC_6H_4	4-$MeOC_6H_4$	81
8	**5h**	Ph	4-ClC_6H_4	87
9	**5i**	4-MeC_6H_4	4-ClC_6H_4	83
10	**5j**	4-ClC_6H_4	4-ClC_6H_4	81
11	**5k**	Ph	4-BrC_6H_4	82
12	**5l**	4-$EtOC_6H_4$	Ph	79
13	**5m**	4-FC_6H_4	Ph	76
14	**5n**	4-$MeOC_6H_4$	Ph	82
15	**5o**	4-MeC_6H_4	*t*-Bu	78
16	**5p**	Ph	*t*-Bu	72

[a] Isolated yields based on acids **2**.

A possible mechanism for the catalytic aza-Wittig transformation of **4** to **5** is proposed (Scheme 3). It presumably involves (i) a metathesis reaction of isocyanate **4** with phospholene oxide **A** to give the iminophosphorane **6** and carbon dioxide;[20] (ii) intramolecular aza-Wittig reaction of iminophosphorane **6** through the carbonyl group to produce 1,4-benzodiazepin-5-one **5** and phospholene oxide **A**, which enters a new catalytic cycle.

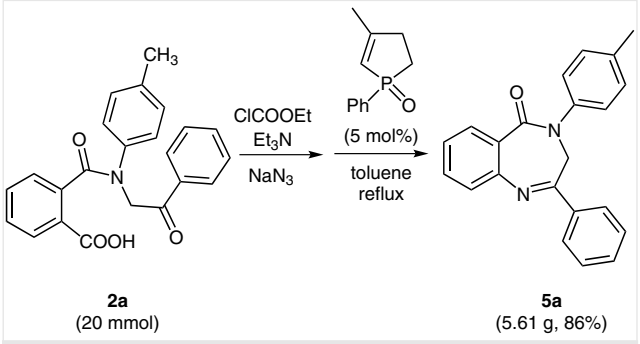


Scheme 3 Possible mechanism for formation of **5**

As a comparison, the cyclization reaction of isocyanate **4** under the conventional hydrolysis/dehydration condition[21] was further investigated (Scheme 4). When the isocyanate **4k** or **4o** was treated with formic acid/4-(dimethylamino)pyridine instead of phospholene oxide **A**, a mixture of amine **7k** or **7o** and 1,4-benzodiazepin-5-one **5k** or **5o** resulted and the 1,4-benzodiazepin-5-ones **5k** or **5o** were only obtained as minor products (28–33%), which implies the advantage of the above catalytic aza-Wittig reaction in the preparation of the cyclic compounds.

To evaluate the applicability of the above catalytic aza-Wittig reaction on a larger scale, we successfully prepared **5a** on a gram scale in a satisfactory 86% yield, and the catalyst was recovered in 95% yield (Scheme 5).

In conclusion, we have developed an efficient synthesis of 1,4-benzodiazepin-5-ones via catalytic aza-Wittig reaction. Owning to the high atom efficiency, the mild reaction conditions, the good yields, and the easily available starting materials, we think that this new approach has potential in the preparation of various 1,4-benzodiazepin-5-ones that are of considerable interest as potential biologically active compounds or pharmaceuticals.

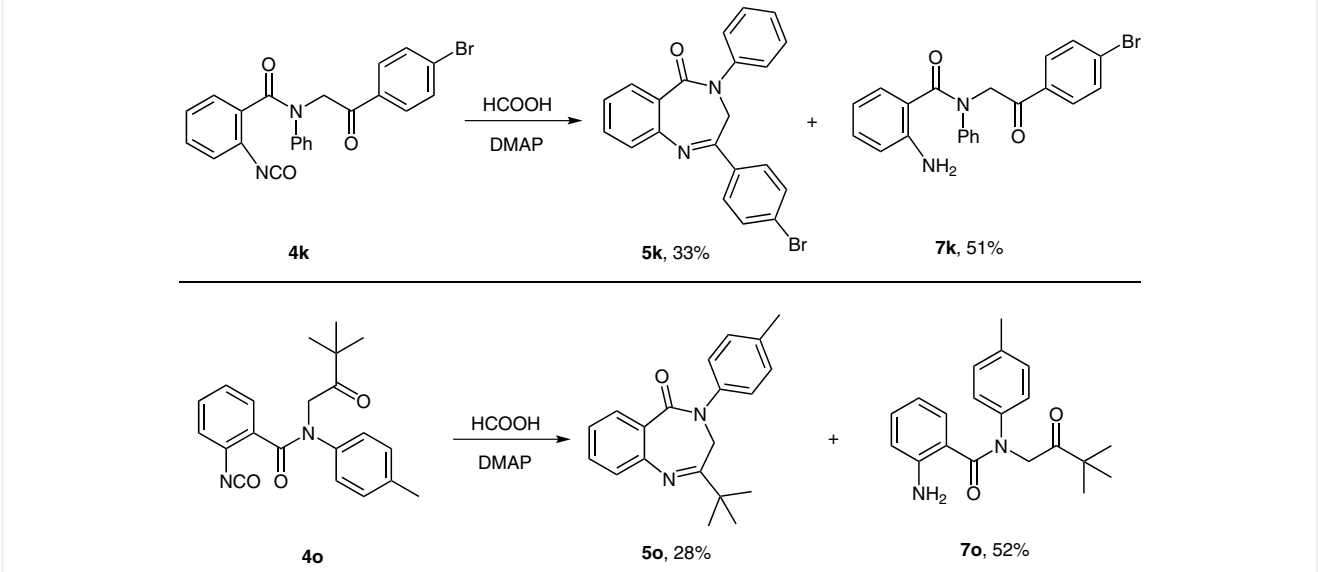


Scheme 5 Preparation of **5a** on a larger scale

Melting points were determined using a X-4 model apparatus and are uncorrected. MS were measured on a Finnigan Trace MS spectrometer. NMR were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 600 or 400 spectrometer and resonances relative to TMS. Elemental analyses were taken on a Vario EL III elementary analysis instrument.

3,4-Dihydro-5*H*-1,4-benzodiazepin-5-ones 5a–p; General Procedure

To a solution of carboxylic acid **2**[18] (1 mmol) in anhyd THF (10 mL) at –10 °C was added dropwise Et_3N (0.11 g, 1.1 mmol), followed by the addition of ethyl chloroformate (0.12 g, 1.1 mmol) over 30 min; the mixture was stirred at –10 °C for 1 h. Then a solution of NaN_3 (0.072 g, 1.1 mmol) in water (1 mL) was added dropwise and the mixture



Scheme 4 Cyclization reaction of isocyanate **4** under conventional hydrolysis/dehydration conditions

was stirred at –10 °C for 3 h. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with brine, and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure to give crude acyl azide **3**. The crude product **3** was dissolved in toluene (10 mL) and the mixture was heated to 60–70 °C for 0.5 h to form isocyanate intermediate **4**. Then 3-methyl-1-phenyl-2-phospholene 1-oxide (**A**, 0.01 g, 0.05 mmol) was added and the mixture was stirred at 110 °C. When the reaction was complete (4–12 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, Et_2O–petroleum ether, 1:4) to give 3,4-dihydro-5*H*-1,4-benzodiazepin-5-ones **5a**–**p**.

2-Phenyl-4-(*p*-tolyl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5a)

White solid; yield: 0.29 g (89%); mp 228–230 °C.

IR (KBr): 2914, 1649, 1592, 1450, 1341, 1200 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.81 (d, *J* = 7.8 Hz, 2 H, H_{Ar}), 7.61–7.14 (m, 10 H, H_{Ar}), 4.51 (s, 2 H, CH_2), 2.38 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 165.0, 146.5, 139.6, 137.3, 136.2, 131.7, 131.3, 130.9, 130.1, 128.8, 127.7, 127.4, 126.8, 126.4, 126.1, 48.0, 21.1.

MS: *m*/*z* (%) = 326 (M^+, 52), 179 (100), 119 (43), 105 (17).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 81.09; H, 5.37; N, 8.72.

2,4-Diphenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5b)

White solid: yield: 0.27 g (87%); mp 174–176 °C.

IR (KBr): 2918, 1652, 1592, 1405, 1342, 1202 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.78 (d, *J* = 6.6 Hz, 2 H, H_{Ar}), 7.60–7.25 (m, 11 H, H_{Ar}), 4.51 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 165.0, 146.5, 142.1, 136.1, 131.8, 131.3, 130.8, 129.4, 128.8, 127.7, 127.4, 127.3, 126.8, 126.6, 126.1, 47.9.

MS: *m*/*z* (%) = 312 (M^+, 45), 179 (100), 105 (41).

Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.97; H, 5.07; N, 9.04.

4-(4-Chlorophenyl)-2-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5c)

White solid: yield: 0.26 g (75%); mp 240–242 °C.

IR (KBr): 2916, 1653, 1591, 1451, 1342, 1219 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.81 (d, *J* = 7.8 Hz, 2 H, H_{Ar}), 7.61 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.55–7.32 (m, 7 H, H_{Ar}), 7.81 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 4.51 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 164.7, 146.5, 140.5, 135.9, 133.0, 132.0, 131.5, 130.8, 129.6, 128.9, 127.9, 127.6, 126.9, 126.3, 47.7.

MS: *m*/*z* (%) = 346 (M^+, 36), 206 (6), 179 (100), 139 (18).

Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.98; H, 4.27; N, 8.24.

2-Phenyl-4-(*o*-tolyl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5d)

White solid: yield: 0.23 g (71%); mp 113–115 °C.

IR (KBr): 1637, 1596, 1452, 1406, 1219 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.77 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.62–7.14 (m, 10 H, H_{Ar}), 4.49–4.36 (m, 2 H, CH_2), 2.08 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 165.0, 146.5, 141.3, 136.2, 135.5, 131.7, 131.3, 131.1, 130.8, 128.7, 128.2, 127.5, 127.2, 127.0, 126.8, 126.1, 47.8, 18.0.

MS: *m*/*z* (%) = 326 (M^+, 58), 309 (13), 221 (17), 179 (100), 118 (23), 105 (26).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 81.14; H, 5.41; N, 8.57.

4-(3-Chlorophenyl)-2-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5e)

White solid: yield: 0.25 g (72%); mp 118–120 °C.

IR (KBr): 3066, 1640, 1590, 1401, 1340, 1201 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.80 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.62–7.14 (m, 10 H, H_{Ar}), 4.50 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 164.7, 146.5, 143.0, 135.9, 134.8, 132.0, 131.5, 130.8, 130.3, 128.9, 127.7, 127.6, 126.9, 126.8, 126.2, 124.8, 47.6.

MS: *m*/*z* (%) = 346 (M^+, 28), 207 (8), 179 (100), 103 (12), 76 (13).

Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.81; H, 4.32; N, 8.27.

2-(4-Methoxyphenyl)-4-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5f)

White solid: yield: 0.28 g (82%); mp 148–150 °C.

IR (KBr): 1646, 1591, 1454, 1259, 1178 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.76 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 7.58 (t, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.45–7.28 (m, 5 H, H_{Ar}), 7.27 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 6.89 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 4.49 (s, 2 H, CH_2), 3.83 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 164.1, 162.2, 146.8, 142.1, 131.7, 130.8, 129.7, 129.5, 129.4, 128.6, 127.4, 127.2, 126.7, 126.6, 125.7, 114.1, 55.3, 47.6.

MS: *m*/*z* (%) = 342 (M^+, 73), 237 (23), 209 (100), 166 (17), 118 (17).

Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.41; H, 5.13; N, 8.22.

2-(4-Methoxyphenyl)-4-(*p*-tolyl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5g)

White solid: yield: 0.29 g (81%); mp 147–149 °C.

IR (KBr): 1646, 1598, 1510, 1386, 1252, 1181 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.78 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.59–7.32 (m, 3 H, H_{Ar}), 7.20 (d, *J* = 7.8 Hz, 2 H, H_{Ar}), 7.13 (d, *J* = 7.8 Hz, 2 H, H_{Ar}), 6.90 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 4.46 (s, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 2.37 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 164.1, 162.1, 146.8, 139.6, 137.2, 131.6, 130.7, 130.0, 129.5, 128.6, 127.3, 126.7, 126.3, 125.6, 114.1, 55.3, 47.7, 21.1.

MS: *m*/*z* (%) = 356 (M^+, 62), 237 (26), 209 (100), 166 (17), 119 (18).

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.58; H, 5.49; N, 7.96.

2-(4-Chlorophenyl)-4-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5h)

White solid: yield: 0.30 g (87%); mp 183–185 °C.

IR (KBr): 3062, 1637, 1586, 1417, 1353, 1088 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.72 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.60 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.45–7.32 (m, 7 H, H_{Ar}), 7.24 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 4.48 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 163.7, 146.2, 141.9, 137.5, 134.4, 131.8, 130.8, 129.5, 129.0, 128.9, 127.5, 127.2, 126.7, 126.4, 126.3, 47.6.

MS: *m*/*z* (%) = 346 (M^+, 71), 213 (100), 178 (49), 151 (18), 105 (88).

Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.96; H, 4.32; N, 8.23.

2-(4-Chlorophenyl)-4-(*p*-tolyl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5i)

White solid: yield: 0.30 g (83%); mp 153–154 °C.

IR (KBr): 1652, 1510, 1387, 1218, 1089 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.74 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.60 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.45–7.37 (m, 4 H, H_{Ar}), 7.21 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.13 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 4.47 (s, 2 H, CH_2), 2.38 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 163.8, 146.2, 139.4, 137.6, 137.5, 134.5, 131.8, 130.9, 130.1, 129.0, 128.9, 127.3, 126.8, 126.3, 126.2, 47.8, 21.1.

MS: *m*/*z* (%) = 360 (M^+, 67), 213 (96), 178 (46), 119 (100).

Anal. Calcd for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.75; N, 7.76. Found: C, 73.35; H, 4.48; N, 7.91.

2,4-Bis(4-chlorophenyl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5j)

White solid: yield: 0.31 g (81%); mp 157–159 °C.

IR (KBr): 3062, 1647, 1589, 1490, 1392, 1091 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.74 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.61 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.45–7.37 (m, 6 H, H_{Ar}), 7.19 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 4.47 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 163.4, 146.2, 140.3, 137.8, 134.2, 133.1, 132.0, 130.8, 129.6, 129.1, 128.8, 127.8, 126.9, 126.8, 126.4, 47.4.

MS: *m*/*z* (%) = 380 (M^+, 34), 243 (15), 213 (100), 178 (46).

Anal. Calcd for $C_{21}H_{14}Cl_2N_2O$: C, 66.16; H, 3.70; N, 7.35. Found: C, 66.44; H, 3.48; N, 7.43.

2-(4-Bromophenyl)-4-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5k)

White solid: yield: 0.32 g (82%); mp 184–186 °C.

IR (KBr): 3060, 1638, 1581, 1447, 1230, 1005 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.66–7.25 (m, 12 H, H_{Ar}), 4.49 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 163.8, 146.2, 141.9, 134.9, 132.0, 131.9, 130.8, 129.5, 129.1, 127.6, 127.2, 126.8, 126.5, 126.4, 126.2, 47.6.

MS: *m*/*z* (%) = 390 (M^+, 54), 259 (91), 178 (45), 105 (100).

Anal. Calcd for $C_{21}H_{15}BrN_2O$: C, 64.46; H, 3.86; N, 7.16. Found: C, 64.51; H, 3.69; N, 7.29.

4-(4-Ethoxyphenyl)-2-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5l)

White solid: yield: 0.28 g (79%); mp 168–170 °C.

IR (KBr): 2978, 1648, 1510, 1449, 1246, 1048 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.81 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.60 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.49–7.35 (m, 5 H, H_{Ar}), 7.16 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 6.91 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 4.83 (s, 2 H, CH_2), 4.05 (q, *J* = 7.2 Hz, 2 H, OCH_2), 1.43 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 165.0, 157.8, 146.4, 136.1, 134.9, 131.6, 131.2, 130.7, 128.7, 127.7, 127.6, 127.3, 126.7, 126.0, 115.1, 63.6, 48.1, 14.7.

MS: *m*/*z* (%) = 356 (M^+, 97), 209 (9), 179 (100), 149 (65), 135 (33).

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.64; H, 5.45; N, 8.01.

4-(4-Fluorophenyl)-2-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5m)

White solid: yield: 0.25 g (76%); mp 191–193 °C.

IR (KBr): 1650, 1508, 1401, 1213, 1154 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.81 (d, *J* = 7.8 Hz, 2 H, H_{Ar}), 7.62 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.51–7.23 (m, 7 H, H_{Ar}), 7.10 (t, *J* = 7.8 Hz, 2 H, H_{Ar}), 4.51 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 164.7, 162.3, 159.9, 146.4, 137.9, 135.8, 131.7, 131.3, 130.6, 128.7, 128.3, 128.2, 127.5, 126.8, 126.7, 126.0, 116.3, 116.0, 47.7.

MS: *m*/*z* (%) = 330 (M^+, 47), 209 (6), 179 (100), 152 (7), 123 (15).

Anal. Calcd for $C_{21}H_{15}FN_2O$: C, 76.35; H, 4.58; N, 8.48. Found: C, 76.61; H, 4.29; N, 8.43.

4-(4-Methoxyphenyl)-2-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5n)

White solid: yield: 0.28 g (82%); mp 159–161 °C.

IR (KBr): 1645, 1511, 1448, 1252, 1025 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.81 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.60 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.49–7.35 (m, 5 H, H_{Ar}), 7.18 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 6.92 (d, *J* = 6.6 Hz, 2 H, H_{Ar}), 4.49 (s, 2 H, CH_2), 3.83 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 165.0, 158.4, 146.4, 136.1, 135.0, 131.6, 131.2, 130.7, 128.7, 127.7, 127.6, 127.3, 126.7, 126.0, 114.6, 55.4, 48.1.

MS: *m*/*z* (%) = 342 (M^+, 94), 209 (10), 179 (100), 152 (11), 135 (52), 121 (35).

Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.14; H, 5.10; N, 8.39.

2-*tert*-Butyl-4-(*p*-tolyl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5o)

White solid: yield: 0.24 g (78%); mp 159–161 °C.

IR (KBr): 2962, 1638, 1451, 1342, 1120 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 7.87 (d, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.60 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.35 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.28–7.22 (m, 5 H, H_{Ar}), 4.14 (br, 2 H, CH_2), 2.33 (s, 3 H, CH_3), 1.04 (s, 9 H, 3 CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.7, 166.1, 145.9, 139.5, 135.8, 131.7, 130.3, 129.2, 127.0, 126.5, 126.3, 125.6, 46.4, 39.0, 27.0, 20.6.

MS: *m*/*z* (%) = 307 (M^+ + 1, 40), 272 (21), 256 (22), 211 (41), 144 (100).

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.62; H, 7.17; N, 9.28.

2-*tert*-Butyl-4-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (5p)

White solid: yield: 0.21 g (72%); mp 140–142 °C.

IR (KBr): 2964, 1641, 1449, 1348, 1200 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 7.87 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 7.61 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.45–7.28 (m, 7 H, H_{Ar}), 4.16 (br, 2 H, CH_2), 1.04 (s, 9 H, 3 CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.7, 166.1, 145.9, 141.9, 131.8, 130.3, 128.7, 127.0, 126.6, 126.5, 126.4, 125.6, 46.4, 39.0, 26.9.

MS: *m*/*z* (%) = 292 (M^+, 100), 235 (27), 187 (62), 159 (59), 144 (46), 103 (63).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.21; H, 6.74; N, 9.47.

Conventional Hydrolysis/Dehydration of Isocyanates 4k and 4o

To the isocyanate **4k** or **4o** prepared as above in toluene, was added formic acid (0.092 g, 2 mmol) and DMAP (0.037 g, 0.3 mmol). The mixture was stirred at 110 °C for 12 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, Et_2O–petroleum ether, 1:4) to give 3,4-dihydro-5*H*-1,4-benzodiazepin-5-one **5k** (0.13 g, 33%) or **5o** (0.086 g, 28%) and amine **7**.

2-Amino-*N*-(2-(4-bromophenyl)-2-oxoethyl)-*N*-phenylbenzamide (7k)

White solid: yield: 0.21 g (51%); mp 150–152 °C.

IR (KBr): 3350, 1705, 1639, 1584, 1511, 1374, 1219 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 9.38–9.14 (m, 1 H, NH), 8.49 (s, 1 H, NH), 8.26 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.90 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.67 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.36–6.88 (m, 8 H, H_{Ar}), 5.33 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 169.5, 159.3, 142.5, 135.2, 133.1, 132.2, 130.6, 129.6, 129.5, 129.1, 127.3, 126.3, 124.2, 123.2, 121.4, 57.0.

MS: *m*/*z* (%) = 410 (M^+, 7), 329 (23), 288 (76), 120 (100).

Anal. Calcd for $C_{21}H_{17}BrN_2O_2$: C, 61.63; H, 4.19; N, 6.84. Found: C, 61.39; H, 4.17; N, 6.91.

2-Amino-*N*-(3,3-dimethyl-2-oxobutyl)-*N*-(*p*-tolyl)benzamide (7o)

White solid: yield: 0.17 g (52%); mp 206–208 °C.

IR (KBr): 3365, 2969, 1718, 1634, 1511, 1291 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.80 (s, 1 H, NH), 7.97 (d, *J* = 8.4 Hz, 1 H, NH), 7.26–6.82 (m, 8 H, H_{Ar}), 4.89 (s, 2 H, CH_2), 2.21 (s, 3 H, CH_3), 1.31 (s, 9 H, 3 CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 210.0, 168.4, 152.3, 140.6, 136.4, 135.7, 129.5, 129.3, 128.6, 126.8, 126.2, 121.9, 55.0, 42.8, 26.0, 20.5.

MS: *m*/*z* (%) = 324 (M^+, 5), 265 (30), 205 (16), 146 (100), 120 (93).

Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.09; H, 7.32; N, 8.90.

Larger-Scale Preparation of 3,4-Dihydro-5*H*-1,4-benzodiazepin-5-one (5a)

To a solution of carboxylic acid **2a** (7.46 g, 20 mmol) in anhyd THF (100 mL) at –10 °C was added dropwise Et_3N (2.22 g, 22 mmol), followed by the addition of ethyl chloroformate (2.39 g, 22 mmol) over 30 min; the mixture was stirred at –10 °C for 1 h. Then a solution of NaN_3 (1.43 g, 22 mmol) in water (10 mL) was added dropwise and the mixture was stirred at –10 °C for 3 h. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, washed with brine, and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure to give crude acyl azide **3a**. The crude product **3a** was dissolved in toluene (100 mL) and the mixture was heated to 60–70 °C for 0.5 h to form isocyanate intermediate **4a**. Then 3-methyl-1-phenyl-2-phospholene 1-oxide (**A**, 0.192 g, 1 mmol) was added and the mixture was stirred at 110 °C. When the reaction was complete (6 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, Et_2O–petroleum ether, 1:4) to give 3,4-dihydro-5*H*-1,4-benzodiazepin-5-one **5a** (5.61 g, 86%) along with the phosphine catalyst **A** (0.182 g, 95% recovery).

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Supporting Information

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