A novel reductive cross-coupling reaction of 2-nitrobenzoic hydrazides and aldehydes or ketones promoted by the low-valence titanium reagent: an access to 2,3,4,5-tetrahydro-1*H*-1,3,4-benzotriazepine-5-one derivatives

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A short and facile synthesis of a series of 2,3,4,5-tetrahydro-1*H*-1,3,4-benzotriazepine-5-one derivatives was accomplished in good yields via the intermolecular reductive coupling reaction of 2-nitrobenzoic hydrazides and aldehydes or ketones promoted by the low-valence titanium reagent ($TiCl_4$/Zn system). Structures were established on the basis of elemental analysis, IR and ^{1}H NMR spectra.

Keywords: 1,3,4-benzotriazepine-5-one, low-valence titanium reagent, 2-nitrobenzoic hydrazide, aldehyde, ketone

In recent years an increasing interest in the reactions induced by a low-valence titanium reagent has occurred because of its exceeding high efficacy in the reductive coupling of carbonyl compounds.[1] A variety of other functional groups can also react.[2-5] Recently, we have reported the low-valence titanium induced intermolecular reductive coupling reaction of carboxylic derivatives with aromatic ketones,[6] the inter-molecular reductive coupling reaction of 4, 4-dicyano-1,3-diaryl-1-butanone[7] and the cyclodimerisation of α,β-unsaturated ketones.[8]

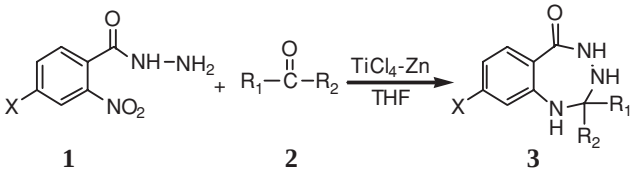
Benzene-fused seven-membered heterocycles such as 1,3, 4-benzotriazepines are important components of a number of pharmacologically active compounds.[9-14] It has been reported that 1,3,4-benzotriazepine analogues have psychostimulant, antidepressant, anorexigenic and antihypertensive properties.[15-18] Various methods are known for the synthesis of 1,3,4-benzotriazepine derivatives, but most of these methods have disadvantages such as harsh reaction conditions and laborious manipulation. In the course of our work on the application of low-valence titanium reagents in the preparation of bioactive heterocyclic compounds, we have reported the synthesis of indoles,[19] 2-amino-quinolines,[4] 2-arylquinolines,[20] quinazolin-4(3*H*)-ones,[21] imidazo[1,2-*c*]quinazolines[22] and pyrroles[23] with the aid of a low-valent titanium reagent. Here we wish to describe a method induced by the $TiCl_4$/Zn system for the preparation of 2,3,4,5-tetrahydro-1*H*-1,3, 4-benzo-triazepines using 2-nitrobenzoic hydrazides and aldehydes or ketones as the starting materials.

When 2-nitrobenzoic hydrazides (**1**) and aldehydes or ketones (**2**) were treated with low-valence titanium, prepared from titanium tetrachloride and zinc powder in anhydrous THF, the reductive cyclisation products, 2,3,4,5-tetrahydro-1*H*-1,3,4-benzotriazepine-5-ones, (**3**) were obtained in good yields (Scheme 1). The results are summarised in Table 1.

The reaction of 2-nitrobenzoic hydrazides (**1**) and the cyclic ketones (**4**) with the same reagent afforded 2,2-polymethylene-2,3,4,5-tetrahydro-1,3,4-benzo- triazepine-5-ones (**5**) (Scheme 2) and the results are summarised in Table 2. However, 2-nitrobenzoic hydrazides failed to react with acetophenone or 1-tetralone to give the analogous products under these reaction conditions.

Moreover, treatment of bis(2-nitrobenzoic hydrazide) (**6**) and acetone (**7**) with $TiCl_4$/Zn in anhydrous THF under the same reaction conditions afforded bis(quinazolin-4(3H)-one) (**8**) in 69 % yield (Scheme 3).

The structure of **3**, **5** and **8** were confirmed by IR, ^{1}H NMR and elemental analysis. In summary, a series of 2,3,4, 5-tetrahydro-1*H*-1,3,4-benzotriazepines were synthesised via reductive cyclisation induced by the $TiCl_4$/Zn system of 2-nitrobenzoic hydrazides with aldehydes or ketones. The advantages of our method are easily accessible starting materials, convenient manipulation and moderate yields.

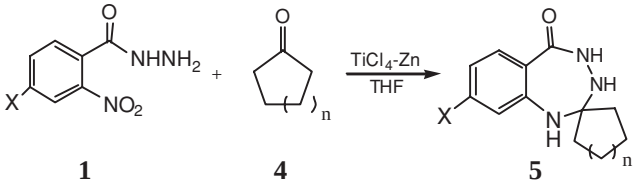


1 **2** **3**

Scheme 1

Table 1 The synthesis of 2,3,4,5-tetrahydro-1H-1,3,4-benzotriazepine-5-ones promoted by low-valence titanium reagent

Entry	Compound	X	R_1	R_2	Isolated yield/%
1	**3a**	H	4-$CH_3C_6H_4$	H	70
2	**3b**	H	4-$CH_3OC_6H_4$	H	75
3	**3c**	H	4-FC_6H_4	H	77
4	**3d**	H	4-ClC_6H_4	H	80
5	**3e**	H	4-BrC_6H_4	H	76
6	**3f**	H	CH_3	CH_3	74
7	**3g**	Cl	CH_3	CH_3	82



1 **4** **5**

Scheme 2

Table 2 The reductive cyclisation of 2-nitrobenzoic hydrazides and cyclic ketones

Entry	Compound	X	*n*	Isolated yield/%
1	**5a**	H	1	71
2	**5b**	H	2	80
3	**5c**	Cl	1	68
4	**5d**	Cl	2	82

Experimental

Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All reactions were performed under a nitrogen atmosphere. Melting points were uncorrected. ^{1}H NMR and

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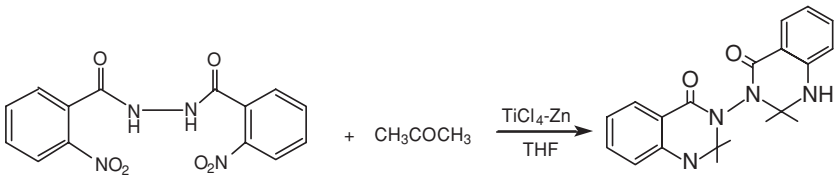

6 **7** **8**

Scheme 3

^{13}C NMR spectra were obtained for solution in $CDCl_3$ or DMSO-d_6 with Me_4Si as internal standard using an Inova-400 MHz spectrometer. Microanalyses were carried out using a Perkin-Elmer 2400 II analyser. IR spectra were recorded on an FT IR-8101 spectrometer in KBr.

*General procedure for the synthesis of 2,3,4,5-tetrahydro-1H-1,3,4-benzo-triazepines (***3** *and* **5***)*

$TiCl_4$ (1.1 ml, 10 mmol) was added dropwise using a syringe to a stirred suspension of zinc dust (1.3 g, 20 mmol) in freshly distilled anhydrous THF (20 ml) at room temperature under a dry nitrogen atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valence titanium reagent formed was cooled to room temperature and a solution of 2-nitrobenzoic hydrazides (3 mmol) and aromatic aldehydes or ketones or cyclic ketones (3 mmol) in THF (10 ml) was added dropwise. The mixture was stirred for 3–4 h at room temperature under N_2 (the reaction was monitored by TLC). The reaction mixture was quenched with 10 % HCl (50 ml) and extracted with $ClCH_2CH_2Cl$ (3 × 50 ml). The combined extracts were washed with water (3 × 50 ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products **3a–g** and **5a–d** were purified by recrystallisation from 95 % ethanol.

The AA'xx' systems in the ^{1}H NMR spectra of **3a–3e** appear as pairs of doublets.

2-(4-Methylphenyl)-2,3,4,5-tetrahydro-1H-1,3,4-benzotriazepine (**3a**): M.p. 215–216 °C. IR: ν/cm^{-1} 3434, 3308, 3188, 3065, 2936, 1655, 1610, 1509, 1484, 1434, 1411, 1384, 1325, 1292, 1152, 1092, 1016, 836, 799, 752. ^{1}H NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 5.88 (1H, s, C^2–H), 5.92 (1H, s, NH), 6.67 (1H, d, *J* = 7.2 Hz, C^9–H), 6.91 (1H, t, *J* = 7.2 Hz, C^8–H), 7.25 (2H, d, *J* = 8.4 Hz, C$^{3'}$–H, C$^{5'}$–H), 7.35 (1H, t, *J* = 7.2 Hz, C^7–H), 7.48 (2H, d, *J* = 8.4 Hz, C$^{2'}$–H, C$^{6'}$–H), 7.95 (1H, d, *J* = 7.2 Hz, C^6–H). Anal. calcd for $C_{15}H_{15}N_3O$: C 71.1, H 6.0, N 16.6; found: C 71.4, H 5.7, N 16.4 %.

2-(4-Methoxylphenyl)-2,3,4,5-tetrahydro-1H-1,3,4-benzotriaz-epine (**3b**): M.p. 209–211 °C . IR: ν/cm^{-1} 3420, 3334, 3165, 2963, 2934, 2837, 1655, 1627, 1605, 1570, 1512, 1487, 1459, 1441, 1421, 1356, 1305, 1291, 1251, 1172, 1157, 1134, 1030, 963, 906, 833, 757, 696. ^{1}H NMR (DMSO–d_6) δ: 3.82 (3H, s, CH_3O), 6.23 (1H, s, C^2–H), 6.68 (1H, d, C^9–H), 6.83 (2H, d, *J* = 8.8 Hz, C$^{3'}$–H, C$^{5'}$–H), 6.90 (1H, t, *J* = 7.2 Hz, C^8–H), 7.32 (1H, t, *J* = 7.2 Hz, C^7–H), 7.39 (2H, d, *J* = 8.8 Hz, C$^{2'}$–H, C$^{6'}$–H), 7.98 (1H, d, *J* = 7.2 Hz, C^6–H), 9.03 (1H, s, NH). Anal. calcd for $C_{15}H_{15}N_3O_2$: C 66.9, H 5.6, N 15.6; found: C 67.0, H 5.7, N 15.4 %.

2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-1H-1,3,4-benzotriazepine (**3c**): M.p. 179–180 °C. IR: ν/cm^{-1} 3448, 3345, 3173, 2822, 1656, 1634, 1612, 1543, 1509, 1499, 1487, 1436, 1368, 1345, 1296, 1232, 1154, 1095, 1015, 965, 870, 858, 837, 795, 782, 752, 699. ^{1}H NMR (DMSO–d_6) δ: 6.27 (1H, s, C^2–H), 6.72 (1H, d, *J* = 7.6 Hz, C^9–H), 6.93 (1H, t, *J* = 7.6 Hz, C^8–H), 7.35 (1H, t, *J* = 7.6 Hz, C^7–H), 7.46 (2H, d, *J* = 8.4 Hz, C$^{2'}$–H, C$^{6'}$–H), 7.61 (2H, d, *J* = 8.4 Hz, C$^{3'}$–H, C$^{5'}$–H), 7.92 (1H, d, *J* = 7.6 Hz, C^6–H), 9.22 (1H, s, NH). ^{13}C NMR (DMSO–d_6) δ 72.0, 115.3, 115.6, 115.8, 116.3, 116.5, 118.4, 128.6, 129.0, 130.1, 136.7, 146.6, 151.5, 161.1. MS (*m/z*): 242 (58.5 %), 147 (100 %). Anal. calcd for $C_{14}H_{12}FN_3O$: C 65.4, H 4.7, N 16.3; found: C 65.5, H 4.65, N 16.4 %.

2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-1H-1,3,4-benzotriazepine (**3d**): M. p. 208–209 °C. IR: ν/cm^{-1} 3448, 3309, 3190, 3066, 2937, 1655, 1610, 1509, 1485, 1434, 1385, 1293, 1152, 1092, 1016, 836, 800, 752, 668. ^{1}H NMR ($CDCl_3$) δ: 5.91 (2H, s, NH, C^2–H), 6.68 (1H, d, *J* = 7.2 Hz, C^9–H), 6.93 (1H, t, *J* = 7.2 Hz, C^8–H), 7.36 (1H, t, *J* = 7.2 Hz, C^7–H), 7.43 (2H, d, *J* = 8.8 Hz, C$^{2'}$–H, C$^{6'}$–H), 7.55 (2H, d, *J* = 8.8 Hz, C$^{3'}$–H, C$^{5'}$–H), 7.94 (1H, d, *J* = 7.2 Hz, C^6–H). ^{13}C NMR (DMSO–d_6) δ: 66.2, 114.9, 115.4, 117.7, 127.8, 128.8, 129.2, 133.4, 133.8, 141.1, 146.1, 163.9. MS (*m/z*): 258 (30.4 %), 147 (100 %). Anal. calcd for $C_{14}H_{12}ClN_3O$: C 61.4, H 4.4, N 15.35; found: C 61.6, H 4.2, N 15.1 %.

2-(4-Bromophenyl)-2,3,4,5-tetrahydro-1H-1,3,4-benzotriazepine (**3e**): M.p. 202–203 °C. IR: ν/cm^{-1} 3448, 3310, 3192, 3065, 2936, 1655, 1608, 1508, 1484, 1432, 1384, 1292, 1152, 1073, 1014, 843, 796, 752. ^{1}H NMR ($CDCl_3$) δ: 5.92 (1H, s, C^2–H), 6.43 (1H, s, NH), 6.69 (1H, d, *J* = 7.2 Hz, C^9–H), 6.94 (1H, t, *J* = 7.2 Hz, C^8–H), 7.38 (1H, t, *J* = 7.2 Hz, C^7–H), 7.49 (2H, d, *J* = 8.0 Hz, C$^{2'}$–H, C$^{6'}$–H), 7.60 (2H, d, *J* = 8.0 Hz, C$^{3'}$–H, C$^{5'}$–H), 7.94 (1H, d, *J* = 7.2 Hz, C^6–H). ^{13}C NMR (DMSO–d_6) δ: 66.3, 114.9, 115.4, 117.8, 122.0, 127.8, 129.5, 131.7, 133.9, 141.6, 148.1, 163.9. MS (*m/z*): 302 (57.2 %), 147 (100 %). Anal. calcd for $C_{14}H_{12}BrN_3O$: C 52.85, H 3.8, N 13.2; found: C 53.0, H 3.6, N 13.2 %.

2,2-Dimethyl-2,3,4,5-tetrahydro-1H-1,3,4-benzotriazepine (**3f**): M.p. 183–184 °C. IR: ν/cm^{-1} 3262, 2970, 1630, 1614, 1586, 1518, 1487, 1464, 1437, 1424, 1381, 1349, 1275, 1264, 1187, 1031, 948, 892, 857, 747, 692. ^{1}H NMR ($CDCl_3$) δ: 1.56 (6H, s, 2 × CH_3), 6.09 (1H, s, NH), 6.63 (1H, d, *J* = 7.2 Hz, C^9–H), 6.84 (1H, t, *J* = 7.2 Hz, C^8–H), 7.31 (1H, t, *J* = 7.2 Hz, C^7–H), 7.88 (1H, d, *J* = 7.2 Hz, C^6–H). ^{13}C NMR (DMSO–d_6) δ: 20.7, 74.4, 114.8, 117.4, 128.0, 133.7, 146.5, 158.8, 172.6. Anal. calcd for $C_{10}H_{13}N_3O$: C 62.8, H 6.85, N 22.0; found: C 63.1, H 6.6, N 21.75 %.

8-Chloro-2,2-dimethyl-2,3,4,5-tetrahydro-1H-1,3,4-benzotriaz-epine (**3g**): M.p. 236–237 °C. IR: ν/cm^{-1} 3240, 3074, 3005, 2973, 1627, 1606, 1577, 1509, 1483, 1458, 1409, 1383, 1360, 1349, 1327, 1283, 1255, 1191, 1165, 1078, 987, 960, 900, 851, 766, 700. ^{1}H NMR ($CDCl_3$) δ: 1.58 (6H, s, 2 × CH_3), 6.60 (1H, s, C^9–H), 6.65 (1H, s, NH), 6.79 (1H, d, *J* = 7.2 Hz, C^7–H), 7.82 (1H, d, *J* = 7.2 Hz, C^6–H). Anal. calcd for $C_{10}H_{12}ClN_3O$: C 53.2, H 5.4, N 18.6; found: C 53.4, H 5.3, N 18.7 %.

2,2-Tetramethylene-2,3,4,5-tetrahydro-1H-1,3,4-benzotriazepine (**5a**): M.p. 261–262 °C. IR: ν/cm^{-1} 3298, 3166, 3001, 2972, 2941, 1638, 1615, 1517, 1485, 1431, 1384, 1333, 1322, 1271, 1149, 1131, 1049, 803, 780, 754. ^{1}H NMR ($CDCl_3$) δ: 1.78–1.80 (4H, m, 2 × CH_2), 1.85–2.00 (4H, m, 2 × CH_2), 6.20 (1H, s, NH), 6.65 (1H, d, *J* = 7.2 Hz, C^9–H), 6.85 (1H, t, *J* = 7.2 Hz, C^8–H), 7.31 (1H, t, *J* = 7.2 Hz, C^7–H), 7.88 (1H, d, *J* = 7.2 Hz, C^6–H). ^{13}C NMR (DMSO–d_6) δ: 22.4, 40.9, 77.7, 113.7, 113.8, 116.9, 129.7, 138.0, 148.9, 163.0. Anal. calcd for $C_{12}H_{15}N_3O$: C 66.3, H 7.0, N 19.3; found: C 66.6, H 6.8, N 19.5 %.

2,2-Pentamethylene-2,3,4,5-tetrahydro-1H-1,3,4-benzotriazepine (**5b**): M.p. 227–228 °C. IR: ν/cm^{-1} 3321, 3060, 3002, 2934, 2856, 1626, 1508, 1488, 1431, 1364, 1351, 1328, 1271, 1208, 1127, 1072, 1042, 1002, 955, 905, 863, 756, 699. ^{1}H NMR ($CDCl_3$) δ: 1.30–1.50 (2H m, CH_2), 1.61–1.72 (4H, m, 2 × CH_2), 1.81–1.98 (4H, m, 2 × CH_2), 4.60 (1H, s, NH), 6.69 (1H, d, *J* = 7.2 Hz, C^9–H), 6.84 (1H, t, *J* = 7.2 Hz, C^8–H), 7.29 (1H, t, *J* = 7.2 Hz, C^7–H), 7.88 (1H, d, *J* = 7.2 Hz, C^6–H). Anal. calcd for $C_{13}H_{17}N_3O$: C 67.5, H 7.4, N 18.2; found: C 67.6, H 7.3, N 18.3 %.

8-Chloro-2,2-tetramethylene-2,3,4,5-tetrahydro-1H-1,3, 4-benzotriazepine (**5c**): M.p. 248–249 °C. IR: ν/cm^{-1} 3263, 3181, 3044, 2941, 1643, 1615, 1519, 1481, 1448, 1420, 1362, 1319, 1277, 1154, 1078, 1045, 937, 912, 855, 768. ^{1}H NMR ($CDCl_3$) δ: 1.66–1.88 (4H, m, 2 × CH_2), 1.90–2.00 (4H, m, 2 × CH_2), 6.00 (1H, s, NH), 6.65 (1H, s, C^9–H), 7.80 (1H, d, *J* = 7.6 Hz, C^7–H), 7.81 (1H, d, *J* = 7.6 Hz, C^6–H). Anal. calcd for $C_{12}H_{14}ClN_3O$: C 57.3, H 5.6, N 16.7; found: C 57.4, H 5.5, N 16.6 %.

8-Chloro-2,2-pentamethylene-2,3,4,5-tetrahydro-1H-1,3, 4-benzotriazepine (**5d**): M.p. 270–271 °C. IR: ν/cm^{-1} 3335, 3073, 2922, 2859, 1623, 1605, 1504, 1483, 1468, 1452, 1365, 1330, 1275, 1237, 1177, 1130, 1080, 1035, 1008, 918, 855, 814, 763, 689. ^{1}H NMR ($CDCl_3$) δ: 1.30–1.42 (2H m, CH_2), 1.64–1.74 (4H, m, 2 × CH_2), 1.75–1.96 (4H, m, 2 × CH_2), 4.67 (1H, s, NH), 6.71 (1H, s, C^9–H), 6.79 (1H, d, *J* = 7.6 Hz, C^7–H), 7.82 (1H, d, *J* = 7.6 Hz, C^6–H). Anal. calcd for $C_{13}H_{16}ClN_3O$: C 58.8, H 6.1, N 15.8; found: C 58.5, H 6.5, N 16.1 %.

General procedure for the synthesis of bis(quinazolin–4(3H)–one) (**8**)

$TiCl_4$ (1.1 ml, 10 mmol) was added dropwise using a syringe to a stirred suspension of zinc dust (1.3 g, 20 mmol) in freshly distilled anhydrous THF (20 ml) at room temperature under a dry nitrogen atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valence titanium reagent formed was cooled to room temperature and a solution of bis (2-nitrobenzoic hydrazide) (2 mmol) and acetone (5 mmol) in THF (10 ml) was added dropwise. The mixture was stirred for 4 h at room temperature under N_2 .The reaction mixture was quenched with 10 % HCl (50 ml) and extracted with $ClCH_2CH_2Cl$ (3 × 50 ml). The combined extracts were washed with water (3 × 50 ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product **8** was purified by recrystallisation from 95 % ethanol.

3,3'-Bis(2,2-dimethyl-1,2-dihydroquinazolin-4(3H)-one) (**8**): M.p. 186–187 °C. IR: ν/cm^{-1} 3261, 3195, 3030, 2996, 1634, 1613, 1578, 1520, 1486, 1423, 1391, 1362, 1334, 1279, 1182, 1147, 1032, 970, 855, 751. ^{1}H NMR ($CDCl_3$) δ: 1.57 (12H, s, 4 × CH_3), 6.15 (2H, s, 2 × NH), 6.63 (2H, d, C^8–H, $C^{8'}$–H), 6.84 (2H, t, *J* = 7.2 Hz, C^7–H, $C^{7'}$–H), 7.31 (2H, t, *J* = 7.2 Hz, C^6–H, $C^{6'}$–H), 7.89 (2H, d, *J* = 7.2 Hz, C^5–H, $C^{5'}$–H). Anal. calcd for $C_{20}H_{22}N_4O_2$: C 68.6, H 6.3, N 16.0; found: C 68.7, H 6.1, N 16.1 %.

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