Pergamon

Tetrahedron Letters 42 (2001) 73–75

TETRAHEDRON LETTERS

Simultaneous reduction of the nitro group and the azide group in *o*-nitrophenylazide induced by the $TiCl_4$/Sm system: a novel synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines

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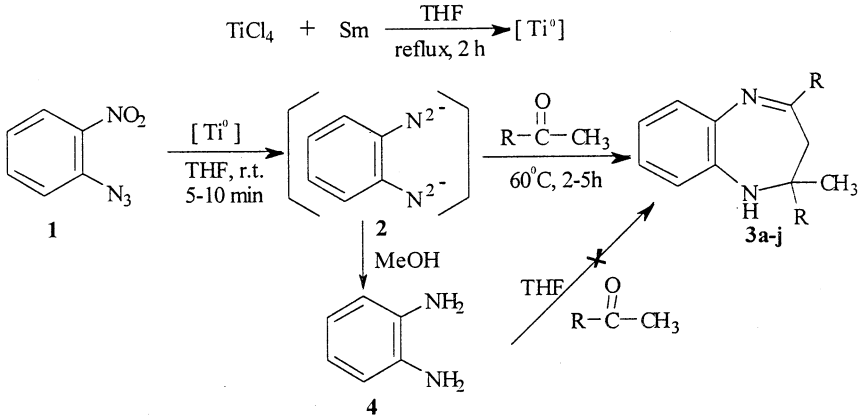
Received 10 August 2000; revised 9 October 2000; accepted 26 October 2000

Abstract—*o*-Nitrophenylazide was treated with the low-valent titanium reagent derived from the $TiCl_4$/Sm system to produce the intermediate **2** in situ, which was a 'living' double-anion and reacted readily with ketones containing active methyl or methylene groups to afford 2,3-dihydro-1*H*-1,5-benzodiazepines in moderate to high yields under mild and neutral conditions.

1*H*-1,5-Benzodiazepine derivatives have attracted strong interest due to their biological properties such as anticonvulsant activity.[1] The method for preparing this kind of compound using *o*-phenylenediamines as starting materials requires harsh conditions such as an acid or base as catalyst, moderate to high thermal conditions and prolonged reaction times, moreover, the yields are relatively low.[2,3] Here we wish to describe a new method induced by the $TiCl_4$/Sm system for the preparation of 2,3-dihydro-1*H*-1,5-benzodiazepines using *o*-nitrophenylazide as the starting material.

It is well known that low-valent titanium reagents have an exceedingly high ability to promote reductive coupling of carbonyl compounds. Many other functional groups can also be reduced by these reagents.[4] Our previous work has shown that the $TiCl_4$/Sm system can induce reduction or coupling reactions.[5] Nitro com-



Scheme 1.

Keywords: titanium tetrachloride; samarium; nitro group; azide; reductive cyclization; 2,3-dihydro-1*H*-1,5-benzodiazepine.
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0040-4039/01/$ - see front matter
PII: S0040-4039(00)01888-8

Table 1. The preparation of 2,3-dihydro-1*H*-1,5-benzodiazepines induced by the $TiCl_4$/Sm system

Entry	R	*T* (h)	Yield (%)[a]
3a	Et	2	78
3a	Et	24	0[b]
3b	*n*-Pr	2	83
3c	*n*-Bu	4	85
3d	*n*-C_5H_{11}	4	65
3e	C_6H_5	1	88
3f	*p*-MeC_6H_4	1	87
3g	*p*-$MeOC_6H_4$	1	89
3h	*p*-ClC_6H_4	3	78
3i	*p*-BrC_6H_4	3	67
3i	*p*-BrC_6H_4	24	0[b]
3j	*m*-$NO_2C_6H_4$	5	56

[a] Isolated yields based on *o*-nitrophenylazide.
[b] MeOH (0.2 mL) was added after the formation of the intermediate **2**. In this case, no products **3** could be detected.

pounds and azide compounds can be easily reduced by low-valent titanium or other reagents;[6] however, they are just reduced to the corresponding amines. Little attention has been paid to reduction intermediates derived from nitro or azide groups by treatment with low-valent titanium reagents, which might induce some reactions difficult to accomplish by other existing methodologies. Recently, we reported the simultaneous reduction of a nitro group and an S–S bond in bis(*o*-nitrophenyl)disulfides induced by the $TiCl_4$/Sm system and its use in the synthesis of some heterocycles containing nitrogen and sulfur.[7] In order to extend the application of the $TiCl_4$/Sm system, we tried the simultaneous reduction of a nitro group and an azide group in *o*-nitrophenylazide using the $TiCl_4$/Sm system. When *o*-nitrophenylazide **1** (1 equiv.) was added dropwise to the low-valent titanium reagent (2.2 equiv.) prepared from samarium powder (3 equiv.) and titanium tetrachloride (2.2 equiv.) in anhydrous THF under reflux, the dark color of the solution gradually changed into a brown–red color. The above phenomenon showed that the nitro group and the azide group had been reduced simultaneously by the low-valent titanium reagent to form the intermediate **2** as a 'living' double-anion in situ. When ketones containing active methyl groups were treated with intermediate **2**, the desired products 2,3-dihydro-1*H*-1,5-benzodiazepines **3** were obtained in good yields (Scheme 1).

When MeOH (0.2 mL) was added to the solution of intermediate **2**, the brown–red color of the mixture immediately turned into a yellow color to afford *o*-phenylenediamine **4**. However, if ketones were added to the solution of **4** under similar conditions, no reaction took place and no products **3** could be detected (entries **3a** and **3i**). Thus the intermediate **2** derived from *o*-nitrophenylazide is more reactive than *o*-phenylenediamine.

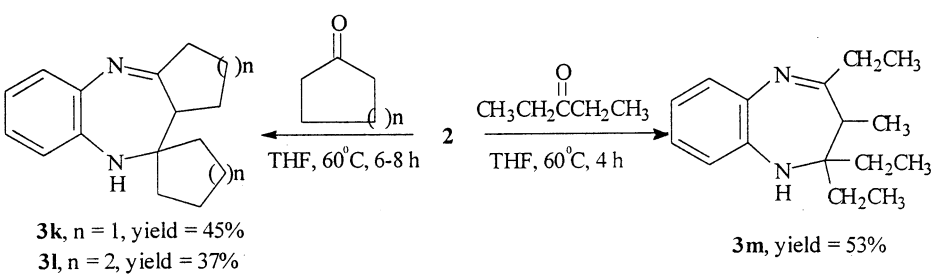
The structures of the products **3** were confirmed by IR, ^1H NMR, MS and elemental analysis.[8,9] The IR spectra of **3a–j** exhibited a sharp band at ~ 3350 cm^{-1} (–NH stretching) and a medium absorption band at ~ 1650 cm^{-1} (C=N). The ^1H NMR spectra of products **3a–d** derived from aliphatic ketones and *o*-nitrophenylazide showed a two-proton singlet at $\delta_H \sim 2.10$ which is due to the methylene group. The ^1H NMR spectra of the corresponding products **3e–j** showed a two-proton single at $\delta_H \sim 2.80$ as for aromatic ketones. On the other hand, in the mass spectra of the products **3a–j**, cyclic 1,5-benzodiazepine ions and benzimidazole ions derived from the fragmentation and skeletal rearrangement of the molecular ions were the main features (Table 1).

Ketones containing an active methylene group such as cyclopentanone, cyclohexanone and 3-pentanone (entries **3k–m**) have been reacted with the intermediate **2** and gave the corresponding products **3** in low to moderate yields (Scheme 2).

In summary, a series of 2,3-dihydro-1*H*-1,5-benzodiazepines was synthesized via reductive cyclization induced by the $TiCl_4$/Sm system of *o*-nitrophenylazide with ketones containing an active methyl or methylene group. The advantages of our method are easily accessible starting materials, convenient manipulation and moderate to high yields.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (Project No. 29872010) and the NSF of Zhejiang province for financial support.



Scheme 2.

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8. General procedure: $TiCl_4$ (0.25 mL, 2.2 mmol) was added dropwise using a syringe to a stirred suspension of Sm powder (0.45 g, 3 mmol) in freshly distilled dry THF (20 mL) at room temperature under a nitrogen atmosphere. After the completion of addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to room temperature and a solution of *o*-nitrophenylazide **1** (1 mmol) in anhydrous THF (2 mL) was added. The deep blue color of the solution changed into a brownish red within 5–10 min. Then ketone (2.2 mmol) in anhydrous THF (2 mL) was added slowly. After stirring at 60°C for a given time (Table 1, the reaction was monitored by TLC), the reaction was quenched with distilled water (10 mL) and extracted with ether (3×30 mL). The organic phase was washed with brine (15 mL) then dried with anhydrous $MgSO_4$. The solvent were removed under reduced pressure to give the crude product which was purified by preparative thick layer chromatography using ethyl acetate and cyclohexane (1:6) as eluant.
9. Typical physical data of compounds are listed. Compound **3c**, **2,4-dibutyl-2,3-dihydro-2-methyl-1*H*-1,5-benzodiazepine** Oil. ν_{max}: 3350 (NH), 2980, 2850, 1475, 1380 (CH_3, CH_2), 1650 (C=N) cm^{-1}. δ_H: 7.23–6.46 (4H, m, ArH), 3.02 (1H, br s, NH), 2.44 (2H, t, $J = 6.5$ Hz, CH_2), 2.06 (2H, s, CH_2), 1.75–0.75 (19H, m, alkyl-H). *m*/*z* (%): 272 (M^+, 13.4), 215 (100), 174 (29.7) and 132 (30.7). Anal. $C_{18}H_{28}N_2$. Calcd C, 79.36; H, 10.36; N, 10.28. Found C, 79.44; H, 10.23; N, 10.09%. Compound **3i**, **2,4-di(4′-bromophenyl)-2,3-dihydro-2-methyl-1*H*-1,5-benzodiazepine**[2a] 152–154°C. ν_{max}: 3350 (NH), 2960, 2830, 1465, 1375 (CH_3, CH_2), 1645 (C=N) cm^{-1}. δ_H: 7.73–6.65 (12H, m, ArH), 3.40 (1H, br s, NH), 2.81 (2H, s, CH_2), 1.58 (3H, s, CH_3). *m*/*z* (%): 472 (M^++4, 9.0), 470 (M^++2, 13.7), 468 (M^+, 7.0), 275 (49), 274 (100), 273 (55.4) and 272 (98.2).