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# An efficient process for the synthesis of *gem*-dinitro compounds under high steric hindrance by nitrosation and oxidation of secondary nitroalkanes

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## ABSTRACT

A new nitrosation and oxidation process to synthesize *gem*-dinitro compounds was accomplished by using nitryl chloride as nitrosation reagent and ozone as oxidizing agent. The main features of the present protocol include the compatibility to substances with high steric hindrance, high yields and mild reaction conditions. A plausible mechanism involving the formation of an intermediate of *gem*-nitrosonitro compound by means of single electron transfer was also proposed.

## Introduction

For centuries, extensive efforts have been devoted to the development of new high energy density materials (HEDMs) that meet the criteria of both higher energy and better safety properties[1-5]. Due to the positive correlation between detonation velocity, detonation pressure, specific impulse and density, the demand for higher energy density is gradually increasing[6]. Currently, there are several known functionalities that can increase the density of energetic compounds, such as nitro, azido, nitroxy, nitramino, difluoramino, *gem*-difluoramino and *gem*-dinitro. It is critical to introduce suitable functionalities with certain number on the skeletons of target energetic compounds due to the inherent contradiction between detonation performance and stability.

Polynitroaliphtic compouds have not found widespread use as either commericial or military explosives up to now because most of them, containing internal *gem*-dinitroaliphatic functionality, have high chemical and thermal stability. But this property is of great importance nowadays owing to the increasing requirement of energetic compounds with low sensitivity and good heat-resistance. Besides, *gem*-dinitro groups can give the energetic compounds higher density and better oxygen balance in comparison with aromatic *C*-nitro compounds.

Although a large number of *gem*-dinitro compouds have been synthesized[7], the methods for efficiently and simply constructing *gem*-dinitro functionality are still limited. Generally, there are two approaches to do this work. One is oxidative nitration of nitroalkanes under basic conditions. For example,

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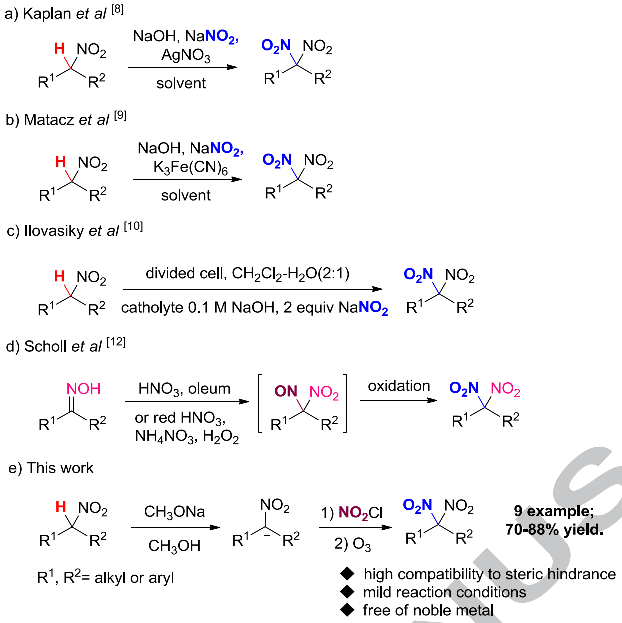


**Scheme 1.** Processes for the synthesis of *gem*-dinitro compounds.

Kaplan and co-workers prepared *gem*-dinitro compounds from sodium nitronates with $AgNO_3/NaNO_2$ through a free radical mechanism (Scheme 1a)[8]. However, this method has the fatal drawback in heavy use of expensive $AgNO_3$ as oxidant. Subsequently, some efforts had been made to use much cheaper oxidants such as stoichiometric potassium ferricyanide or catalytic amount of potassium ferricyanide with stoichiometric amount of persulfate anion as co-oxidant (Scheme 1b), but still no obvious improvement in reaction yield had been achieved[9]. In addition, under electrochemical conditions, sodium nitronates can react directly with sodium nitrite to afford *gem*-nitro compounds (Scheme 1c)[10]. Lister and co-workers improved this process and their following project was to investigate pilot-plant scale reaction[11]. The other approach for constructing *gem*-dinitro functionality is tandem nitrosation-oxidation of oximes by Scholl method[12] *via* the intermediate of pseudonitrole[13] (Scheme 1d).

As potential candidates of HEMDs, polynitroadamantanes have attracted widespread attention[14]. In 1988, the oxidative nitration of nitroadamantanes with $AgNO_3/NaNO_2$ was studied by Archibald and co-workers[15]. For example, 2-nitroadamantane was converted to 2,2-dinitroadamantane in 89% yield while both 2,4-dinitroadamantane and 2,6-dinitroadamantane did not give *gem*-dinitro derivatives by this methods. Meanwhile, direct nitration of 2,4-adamantanedionedioxime resulted in the Nef reaction product 2,4-adamantanedione and the intramolecular ring-closure byproduct 2,4-dinitro-2,4-dinitrosoadamantane[16]. For 2,6-dinitroadamantane, its *gem*-dinitro product 2,2,6,6-tetranitroadamantane can be achieved by reaction in $NaOH/C(NO_2)_4$ system. However, this protocol failed for the case of 2,4-dinitroadamantane. The reason might be assigned to the high steric hindrance. In fact, there are no reports on the synthesis of polynitroadamantanes that contain seven or more nitro groups.

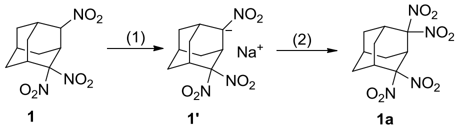
In order to synthesize polynitroadamantanes containing more *gem*-dinitro groups, more efficient processes for introducting *gem*-dinitro functionality to carbons with high steric hindrance are still required. In this paper, an efficient process for the conversion of nitroalkanes to *gem*-dinitro compounds *via* nitrosation with nitryl chloride and oxidation with ozone is reported.

## Results and discussion

Eaton and co-workers[17] tried to synthesize octanitrocubane by direct electrophilic nitration of various alkali salts of heptanitrocubane with $N_2O_4$, $NO_2Cl$, $NO_2BF_4$, $NO_2PF_6$ and some nitrate esters but failed at all. Finally, they accomplished this target through the tandem reactions of nitrosation and oxidation. Some similar reaction process that electrophilic reagents reacted directly with metal salts were also reported[18]. Refer to this method, 2,2,4-trinitoadamantane (**1**) was use as the model substrate to optimize the reaction conditions and the results was listed in Table 1.

Firstly, the oxidative nitration with $AgNO_3/NaNO_2$ was attempted, but no target product 2,2,4,4-tetranitroadamantane (**1a**) was obtained (Table 1, Entry 1). When a large excess of $N_2O_4$ (15 equivalents) was used and the reaction was carried out at -30℃, the green nitrosation intermediate was observed. But unfortunately, the effort to separate it out of the reation mixture failed. After oxidizing with ozone, the target product **1a** was isolated in an overall yield of 35% (Table 1, Entry 2). It was once thought to be an electrophilic reaction between nitrosonium ion ($NO^+$) and carbon anion in the first step. But when NOCl[19] was used as nitrosating reagent, the target product **1a** was obtained in much lower yield of 16% (Table 1, Entry 3). As a result, the formation of pseudonitrole might not be the classical electrophilic nitrosation process. $NO_2BF_4$ and $NO_2Cl$ were used as nitrating agents long before[20]. To our surprise, when highly active nitrating reagents $NO_2BF_4$ or $NO_2Cl$ were applied, the green nitrosation intermediate still formed according to the experimental phenomena. With the inletting of ozone, the green mixture gradually changed to colorless and afforded **1a**. For the case of $NO_2BF_4$, the yied was still very low and comparable to that of NOCl (Table 1, Entry 4). To our delight, the yield was dramatically elevated to 66% when $NO_2Cl$ was applied (Table 1, Entry 5). Increasing the dosage of $NO_2Cl$ from 15 equivalents to 20 equivalents could further improve the yield to 77% (Table 1, Entry 6). More $NO_2Cl$ (25 equiv.) resulted in no obvious change of yield (Table 1, Entry 7). Decreasing the reaction temperature could improve the yield in a certain extent (Table 1, Entries 8 and 9). The yield decreased obviously when the reaction time was shortened to 1 hour (Table 1, Entry 10). Longer time didn't improve the yield (Table1, Entries 11 and 12). From Table 1, the optimum reaction conditions involve the nitrosation of **1** with $NO_2Cl$ (20 equiv.) in $CH_2Cl_2$ at -70℃ for 2 h and the oxidation with ozone (Entry 9).

**Table 1.** Preparation of 2,2,4,4-tetranitroadamantane through nitrosation and oxidation of 2,2,4-trinitroadamantane.[a]

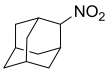
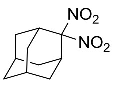


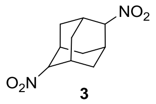
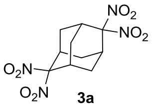
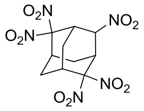
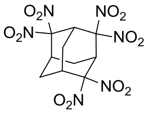
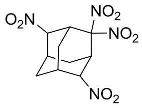
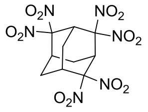
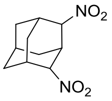
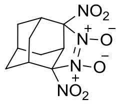
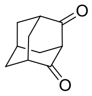
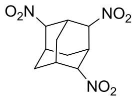
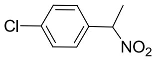
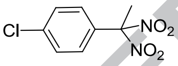
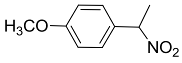
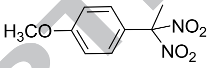
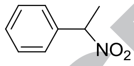
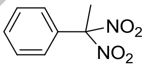
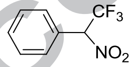
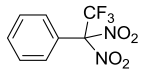
| Entry | Nitrating reagent | Usage [equiv.] | Temperature [℃] | Time [h] | Yield[c] [%] |
|---|---|---|---|---|---|
| 1 | $NaNO_2$[b] | 5 | 20 | 1 | -- |
| 2 | $N_2O_4$ | 15 | -30 | 2 | 35 |
| 3 | NOCl | 15 | -30 | 2 | 16 |
| 4 | $NO_2BF_4$ | 15 | -30 | 2 | 20 |
| 5 | $NO_2Cl$ | 15 | -30 | 2 | 66 |
| 6 | $NO_2Cl$ | 20 | -30 | 2 | 76 |
| 7 | $NO_2Cl$ | 25 | -30 | 2 | 77 |
| 8 | $NO_2Cl$ | 20 | -50 | 2 | 83 |
| 9 | $NO_2Cl$ | 20 | -70 | 2 | 87 |
| 10 | $NO_2Cl$ | 20 | -70 | 1 | 61 |
| 11 | $NO_2Cl$ | 20 | -70 | 3 | 85 |
| 12 | $NO_2Cl$ | 20 | -70 | 4 | 85 |

[a] Reaction conditions: (1) compound **1** (1 mmol), $CH_3ONa$ (1.1 mmol), $CH_3OH$ (5 mL), RT, 4 h; (2) compound **1'**, nitrating or nitrosating reagents, $CH_2Cl_2$ (100 mL); then ozone was bubbled into the system until the system became colourless. [b] $AgNO_3$ (3 mmol, 3 equiv.), ethanol (10 mL), water (10 mL). [c] Isolated yield.

With the optimum conditions in hand, several high sterically hindered secondary nitroalkanes, mainly polynitroadamantanes, were examined. It can be seen from Table 2 that 2-nitroadamantane (**2**) and 2,6-dinitroadamantane (**3**) were smoothly converted to their *gem*-dinitro products in excellent yields (Table 2, Entries 1 and 2). To our deligt, a very high

**Table 2.** Substrate scope for the nitrosation and oxidation tandem process leading to the *gem*-dinitro compounds[a].

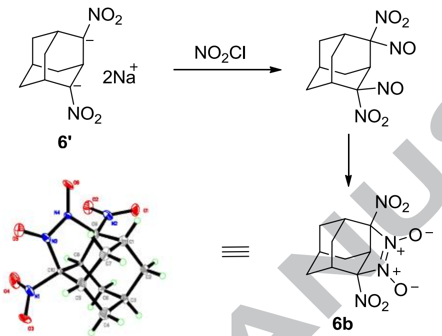
| Entry | Substrate | Product | Yield[b] |
|---|---|---|---|
| 1 |  **2** |  **2a** | 88 |

| | | | |
|---|---|---|---|
| 2 | <br>**3** | <br>**3a** | 82 |
| 3 | <br>**4** | <br>**4a** | 85 |
| 4 | <br>**5** | <br>**4a** | 80 |
| 5 | <br>**6** | <br>**6b**<br><br>**6c** | 40<br>45 |
| 6 | <br>**7** | ND[c] | – |
| 7 | <br>**8** | <br>**8a** | 76 |
| 8 | <br>**9** | <br>**9a** | 83 |
| 9 | <br>**10** | <br>**10a** | 79 |
| 10 | <br>**11** | <br>**11a** | 70 |

[a] Reaction conditions: (1) nitro compound (1 mmol), $CH_3ONa$ (1.1 mmol), $CH_3OH$ (5 mL), RT for 4 h; (2) sodium nitronate (1 mmol), $NO_2Cl$ (20 mmol, 20 equiv.), $CH_2Cl_2$ (100 mL), -70℃ for 2 h, then ozone was bubbled into the system until the system was colourless. [b] Isolated yield. [c] not detected.

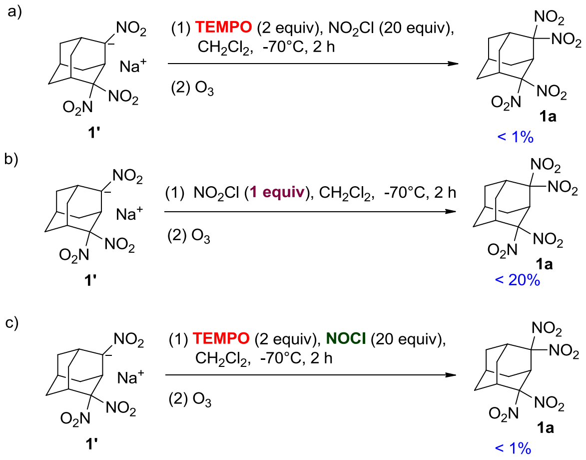
sterically hindered substrate 2,2,4,6,6-pentanitroadamantane (**4**), was very compatible to this method and furnished *gem*-dinitro product 2,2,4,4,6,6-hexanitroadamantane (**4a**) in 85% yield with a little byproduct of Nef reaction, 2,2,6,6-tetranitro-4-adamantanone (Table 2, Entry 3). Similarily, another high sterically hindered substrate 2,4,4,6-tetranitroadamantane (**5**) also gave the target product **4a** in 80% yield (Table 2, Entry 4). Compound **4a** was firstly synthesised by Dave and co-workers[21] from dimethyl malonate and paraformaldehyde *via* a 10-step route in 0.24% overall yield. And in 2014, our group reported an improved strategy by using $N_2O_5$ as nitrating reagent[14c]. As a result, the yield of direct nitration of 2,6-bis(hydroxyimino)-4,4-dinitroadamantane was improved from 21% to 47%, which was still low relatively. By contrast, the new approach was more efficient.

However, when the nitronate anions were on 2,4-positions, the reaction produced no traget products without expection. For example, 2,4-dinitroadamantane (**6**) resulted in an intramocular ring-closure product 2,4-dinitro-2,4-dinitrosoadamantane (**6b**)[15] (Scheme 2) and 2,4-adamantanedione (**6c**) (Table 2, Entry 5). The structure of **6b** was confirmed by X-ray single crystal diffraction and NMR test. The crystal density of **6b** was determined to be 1.64 g cm$^{-3}$, which was a little lower than 2,2,4,4-tetranitroadamantane (1.65 g cm$^{-3}$). The thermal stability of **6b** was determined by differential scanning calorimetry (DSC) and thermogravimetry (TG). The results show that the onset decomposition temperature of **6b** is 166.5℃ while that of 2,2,4,4-tetranitroadamantane is 223.8℃. In addition, the formation of **6b** also supports the fact that the reaction may proceed through nitrosation[22]. For 2,4,6-trinitroadamantane **(7)**, only some unidentified byproducts were obtained (Table 2, Entry 6). In addition, a number of arylnitroalkanes such as *p*-(1-nitroethyl)chlorobenzene, *p*-(1-nitroethyl)anisole, 1-nitroethylbenzene and 1-nitro-2,2,2-trifluoroethylbenzene also proceeded smoothly and afforded the target *gem*-dnitro products with high yields of 76%, 83%, 79%, 70% respectively (Table 2, Entries 7-10).



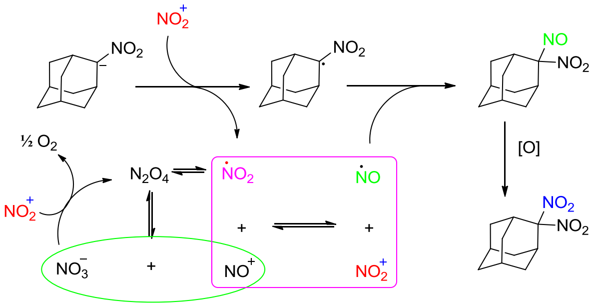
**Scheme 2.** Formation of the intramolecular ring-closure product **6b**.

As mentioned above, the reaction might not be proceed through the classical electrophilic reaction between nitronium ($NO_2^+$) or nitrosonium ion ($NO^+$) and carbon anion. We assumed that the reaction mechanism might involve a single electron transfer process, based on the fact that nitronium ($NO_2^+$) and nitrosonium ion ($NO^+$) have the oxidizing ability[23]. To testify this hypothesis, we added 2 equivalents of TEMPO, a typical free radical trapping agent, into the reaction mixture and no corresponding *gem*-dinitro product could be gotten (Scheme 3a). Decreasing the usage of $NO_2Cl$ from 20 equivalents to 1 equivalent reduced the yield to be less than 20%, indicating an additional consumption of $NO_2Cl$ except reacting with sodium nitronates (Scheme 3b). Similarly, when TEMPO (2 equiv.) was added to the reaction mixture with NOCl as nitrosation reagent, no product was afforded either (Scheme 3c).



**Scheme 3.** Experiments for mechanistic understanding.

Based on the above results, a plausible mechanism for this protocol was postulated (Scheme 4) using 2-nitroadamantane as model substrate. First of all, a single electron transfer reaction happens between the carbon anion and $NO_2^+$ to afford nitroxyl radical and carbon radical. The nitroxyl radical can form dinitrogen tetroxide ($N_2O_4$) which can provide $NO^+$ and nitrate ($NO_3^-$) by heterolysis. In addition, $N_2O_4$ can also be provided from the reaction between $NO_3^-$ and $NO_2^+$ with the release of oxygen. The *gem*-nitrosonitro intermediate comes from the radical coupling between carbon radical and NO free radical arising from the SET reaction between $NO^+$ and nitroxyl radical. At last, the *gem*-nitrosonitro product is oxidized to the *gem*-dinitro derivative with ozone.



**Scheme 4.** Proposed reaction mechanism.

## Conclusions

In conclusion, we reported an efficient method to synthesize *gem*-dinitro compounds from secondary nitroalkanes with nitryl chloride as nitrosating reagent and ozone as oxidizing agent. The nitrosation reaction involves a single electron transfer process. This method is especially suitable for introducing nitro functionality into the secondary nitroalkanes with high steric hindrance.

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## References and notes

1. Agrawal, J. P.; Hodgson, R. D. *Organic Chemistry of Explosives*, Wiley: New York, 2007.
2. Agrawal, J. P. *Prog. Energy Combust. Sci.* **1998**, *24*, 1-30.
3. Giles, J. *Nature*. **2004**, *427*, 580-581.
4. Zhang, Q.; Shreeve, J. M. *Chemical Reviews*. **2014**, *114*, 10527-10574.
5. Klapötke, Thomas M. *Chemistry of High-Energy Materials*, Walter de Gruyter : Berlin-New York, 2011.
6. (a) Kamlet, M. J.; Jacobs, S. J. *J. Chem. Phys.***1968**, *48*, 23-35. (b) Mul, J.; Korting, P.; Schoyer, H. *AIAA*, 1988, 88-3354.
7. (a) Huang, S.; Tian, J.; Qi, X.; Wang, K.; Zhang, Q. *Chem. Eur. J.* **2017**, *23*, 12787-12794. (b) Li, H.; Zhao, F. Q.; Gao, H. X.; Tong, J. F.; Wang, B. Z.; Zhai, L. J.; Huo, H. *Inorganica Chimica Acta*. **2014**, *423*, 256-262. (c) Langlet, A.; Latypov, N. V.; Wellmar, U.; Bemm, U.; Goede, P.; Bergman, J. *J. Org. Chem.* **2002**, *67*, 7833-7838. (d) Axenrod, T.; Guan, X.; Sun, J.; Qi, L.; Chapman, R. D.; Gilardi, R. D. *Tetrahedron Letters.* **2001**, *42, 2621-2623.*
8. Kaplan, R. B.; Shechter, H. *J. Am. Chem. Soc.* **1961**, *83*, 3535-3536.
9. (a) Matacz, Z.; Piotrowska, H.; Urbanski, T. *Pol. J. Chem.* **1979**, *53*, 187-192. (b) Kornblum, N.; Singh, H. K.; Kelly, W. J. *J. Org. Chem.* **1983**, *48*, 332-337. (c) Archibald, T. G.; Garver, L. C.; Baum, K.; Cohen, M. C. *J. Org. Chem.* **1989**, *54*, 2869-2873.
10. Ilovaisky, A. I.; Merkulova, V. M.; Ogibin, Y. N.; Nikishin, G. I. *Russ. Chem. Bull.* **2005**, *54*, 1585-1592.
11. Lister, T. E.; Fox, R. V. *J. Appl. Electrochem*. **2008**, *38*, 523–529.
12. (a) Moiseev, I. K.; Mratkhuzina, T. A.; Balenkova, E. S.; Makarova, N. V. *Russ. J. Org. Chem.* **1999**, *35*, 839-840. (b) Luk'yanov, O. A.; Pokhvisneva, G. V. *Russ. Chem. Bull.* **1991**, *40*, 1906-1908. (c) Scholl, R. *Ber*. **1888**, *21*, 506. (d) Bisgrove, D. E.; Clapp, L. B.; Grabiel, C. E. *J. Am. Chem. Soc.* **1955**, *77*, 1293-1294.
13. (a) Rheinboldt, H.; Dewald, M. *Chem. Ber*. **1927**, *60*, 249-251. (b) Charlton, W.; Earl, J. C.; Kenner, J.; Luciano, A. A. *J. Chem. Soc*. **1932**, *41*, 30-41. (c) Ungnade, H. E.; Kissinger, L. W. *J. Org. Chem*. **1959**, *24*, 666-668. (d) Frojmovic, M. M.; Just, G. *Can. J. Chem*. **1968**, *46*, 3719-3726.
14. (a) Sollott, G. P.; Gilbert, E. E. *J. Org. Chem.* **1980**, *45*, 5405-5408. (b) Dave, P. R.; Ferraro, M.; Ammon, H. L.; Choi, C. S. *J. Org. Chem*. **1990**, *55*, 4459-4461. (c) Ling, Y.; Zhang, P.; Sun, L.; Lai, W.; Luo, J. *Synthesis*. **2014**, *46*, 2225. (d) Ling, Y.; Ren, X.; Lai, W.; Luo, J. *Eur. J. Org. Chem*. **2015**, 1541-1547. (e) Hou, T. J.; Zhang, J.; Wang, C. J.; Luo, J. *Org. Chem. Frontiers*. **2017**, *4*, 1819-1823.
15. Archibald, T. G.; Baum, K. *J. Org. Chem*. **1988**, *53*, 4645-4649.
16. (a) Snyder, J. P.; Heyman, M. L.; Suciu, E. N. *J. Org. Chem*. **1975**, *40*, 1395-1405. (b) Greene, F. D.; Gilbert, K. E. *J. Org. Chem*. **1975**, *40*, 1409-1415. (c) Parmeggiani, C.; Matassini, C.; Cardona, F.; Goti, A. *Synthesis*. **2017**, *49*, 2890-2900. (d) Quek, S. K.; Lyapkalo, I. M.; Han, H. V. *Synthesis*. **2006**, 1423-1426.
17. Zhang, M. X.; Eaton, P. E.; Gilardi, R. *Angew. Chem. Int. Ed*. **2000**, *39*, 401-404.
18. (a) Tani, K.; Lukin, K. A.; Eaton, P. E. *J. Am. Chem. Soc*. **1997**, *119*, 1476-1477. (b) Lukin, K. A.; Li, J. C.; Eaton, P. E.; Kanomate, N.; Hain, J.; Punzalan, E.; Gilardi, R. *J. Am. Chem. Soc*. **1997**, *119*, 9591-9602.
19. Meinwald, J.; Grossman, R. F. *J. Am. Chem. Soc*. **1956**, *78*, 992-995.
20. (a) Price, C. C.; Sears, C. A. *J. Am. Chem. Soc*. **1953**, *75*, 3276-3277. (b)Shechter, H.; Conrad, F.; Daulton, A. L.; Kaplan, R. B. *J. Am. Chem. Soc*. **1952**, *74*, 3052-3056. (c) Olah, G.; Kuhn, S.; Mlinko, A. *J. Chem. Soc*. **1956**, 4257-4258.
21. Dave, P. R.; Bracuti, A.; Axenrod, T.; Liang, B. M. *Tetrahedron*. **1992**, *48*, 5839-5846.
22. (a) Nielsen, A. T. *J. Org. Chem*. **1962**, *27*, 1993-1998. (b) Singh, P. *J. Org. Chem*. **1975**, *40*, 1405-1408.
23. (a) Olah, G. A.; Prakash, G. K. S.; Wang, Q.; Li, X. *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, 2001, DOI: 10.1002/047084289X.rn043. (b) Eisenhofer, A.; Wille, U.; Koenig, B. *Australian Journal of Chemistry*, **2017**, *70*, 407-412.

Highlights:

- High compatibility to secondary nitroalkanes with steric hindrance
- Presence of single electron transfer in nitrosation of nitronates with nitryl chloride
- Mild reaction conditions comparing to Scholl's oxidative *gem*-dinitration of oxime
- Free of noble metal comparing to Shechter- Kaplan oxidative nitration

## Graphical Abstract

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### An efficient process for the synthesis of *gem*-dinitro compounds under high steric hindrance by nitrosation and oxidation of secondary nitroalkanes

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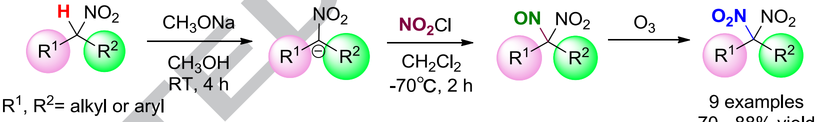
Jian Zhang [a], Tianjiao Hou [a], Yifei Ling [b], Lin Zhang [a*], Jun Luo [a*]



- high compatibility to steric hindrance
- mild reaction conditions
- free of noble metal