Nanometre-sized titanium dioxide-catalyzed reactions of nitric oxide with aliphatic cyclic and aromatic amines†

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Activated on the surface of nanometre-sized TiO_2, NO gas can easily react with aliphatic cyclic amines and aryl free radicals at RT under atmospheric pressure to offer NONOates and cupferron sodiums, respectively.

An increasing knowledge of the role of nitric oxide (NO) in a number of physiological and pathological processes has stimulated efforts to target the NO pathway pharmacologically.[1] Since NO is a pleiotropic molecule, the selective delivery of NO to the specific tissues has recently been attracting much attention, particularly in the field of anticancer therapy.[2] Among the various NO donors that directly or indirectly release NO being used in biomedical research, nitrogen-bound diazen-1-ium-1,2-diolate (formally known as NONOate) is the most important, owing to its ability to deliver NO to some specific tissues.[3] Since access to NONOates generally requires considerably strict conditions, such as special apparatus, low temperature and/or high pressure,[4] a catalytic method is highly desirable. In continuation of our studies on the site-targeting of NO donor drugs,[5] we developed a novel preparative approach of NONOates through nanometre-sized TiO_2-catalyzed reactions of NO with aliphatic cyclic amines at RT under atmospheric pressure, using easily available apparatus. Interestingly, in expanding this new approach to aromatic amines for the preparation of their corresponding NONOates, cupferrons, another kind of useful NO donor, were unexpectedly obtained. Herein, we report these results and propose the mechanisms involved.

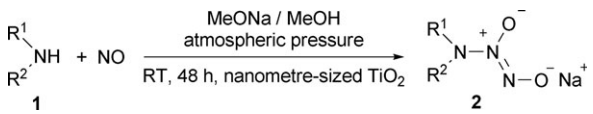
The adsorption of NO onto a single crystal TiO_2(110) surface has been widely utilized in various fields, including pollution control, NO gas sensors and so on.[6a] Some theoretical and experimental studies have already demonstrated the adsorptive and photocatalytic functions of TiO_2 for small inorganic molecules.[6b] Thus, we envisioned that nanometre-sized TiO_2 may act as a catalyst for the preparation of NONOates.

To meet the needs of our NO donor drug research, nine five- or six-membered aliphatic cyclic amines were chosen to conduct the experiments examining the catalytic potential of nanometre-sized TiO_2 (Table 1).

As can be seen, the reactions in the presence of TiO_2 (1.04 mol%) (see the ESI for optimization of the catalyst loading†) gave the products in higher yields (89–96%) than previously reported (33–88%) (Table 1, entries 1, 2, 4, 7 and 8). Several new compounds were also obtained in nearly quantitative yields (Table 1, entries 3, 5, 6 and 9). In order to elucidate the catalytic effect of TiO_2, compounds **2c–2f** were prepared in the presence and absence of TiO_2 under the conditions shown in Table 1, with a reaction time of 5 h. It was found that the product yields in the former case were 52, 50, 72 and 79%, respectively, three- to six-fold higher than those in the latter case (18, 12, 19 and 13%, respectively), indicating that the nanometre-sized TiO_2 does promote the reactions.

All structures of the NONOates obtained by this novel approach were established by ^{1}H NMR and elemental analysis. In addition, the geometry of the N=N double bond of the

Table 1 Nanometre-sized TiO_2-catalyzed reactions of NO with aliphatic cyclic amines[a]



Entry	Aliphatic cyclic amine	Yield (lit. yield) (%)[c]
1	Pyrrolidine (**1a**)	90 (54)[7a]
2	Piperidine (**1b**)	89 (70)[7b]
3	4-Hydroxypiperidine (**1c**)[b]	89
4	*N*-hydroxyethyl piperazine (**1d**)	96 (88)[7c]
5	*N*-methyl piperazine (**1e**)[b]	96
6	*N*-isopropyl piperazine (**1f**)[b]	90
7	*N*-Boc piperazine (**1g**)	92 (42)[7d]
8	*N*-phenyl piperazine (**1h**)	94 (33)[7d]
9	*N*-benzyl piperazine (**1i**)[b]	85

[a] All reactions were run with 1.04 mol% TiO_2; the reaction times were the same as those for the previously reported compounds (24–48 h), and 48 h for the unreported compounds. [b] Unreported compounds. [c] Yield of the isolated product.

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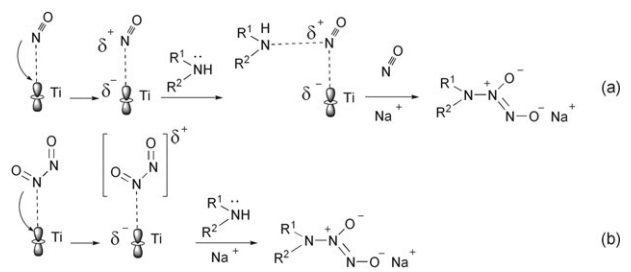
† Electronic supplementary information (ESI) available: Typical experiment procedures and analytical data for the products, as well as crystallographic data for **3i**, **6a** and **3h**. CCDC 705768–705770. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/b820535c

NONOates (Table 1) was determined by single-crystal X-ray diffraction analysis using two representative compounds: **3h** (CCDC 705770†), an O^2-methylated derivative of **2h**, and **3i** (CCDC 705768†), a hydrochloride salt of the O^2-methylated derivative of unreported compound **2i** (recrystallization of NONOates **2** is impossible due to decomposition).[8] In order to elucidate other important characteristics of the NONOates for further medicinal research, NO release and their half-lives *in vitro* were also assayed (see the ESI†).

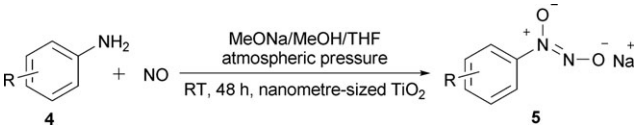
Recently, DeRosa *et al*. reported[9] that high pressure methods for the preparation of NONOates have the disadvantage that NO could react with MeONa in MeOH to form the side product sodium formate. In contrast, under our reaction conditions (Table 1), the side reaction was greatly suppressed and the yield of the side product (only a trace amount) was much lower than previously reported (7.7%). Thanks to this result, MeONa could still be employed as the base when MeOH was used as the solvent in our reactions, instead of the expensive and not easily available sodium trimethylsilanoate.[9]

Next, we tried to propose a plausible mechanism for the TiO_2-catalyzed preparation of NONOates. It is known that NO, as a radical molecule, has one electron in its 2π orbital. This electron can easily transfer to a metal atom's d orbital when NO is adsorbed onto its surface, leading to the formation of a nitrosonium ion NO^+.[6c] When NO is adsorbed onto the surface of TiO_2(110), the preferred configuration might be either a Ti–NO or Ti–*cis*-N_2O_2 orientation[6a] (Scheme 1). Through an analysis of the distribution of electron density in the molecule–slab system, it was found that upon adsorption, there is a clear polarization of NO or N_2O_2, with an increase of the electronic charge in the region between the N and Ti atoms.[6a] It is likely that the adsorption of NO onto the surface of TiO_2(110) could decrease the electron density around the N atom, inducing a certain positive electrical character (δ^+) on the NO or N_2O_2. The mechanism proposed by Drago *et al*. for the formation of NONOates in high pressure reactions of diethylamine with NO demonstrated that the attack of the lone pair electrons of the nitrogen of secondary amines on the NO is the rate determining step.[10] So, the induced δ^+ of NO in our case might accelerate this key step and our proposed mechanism is illustrated in Scheme 1(a). However, an alternative mechanism, the attack of secondary amines on N_2O_2 to generate the NONOates (Scheme 1(b)), could not be excluded, despite the fact that the attack of base on N_2O_2 in the absence of TiO_2 was denied according to the observed kinetic data.[10]



Scheme 1 The proposed mechanisms underlying the nanometre-sized TiO_2-catalyzed reaction of NO with aliphatic cyclic amines.

Table 2 Nanometre-sized TiO_2-catalyzed reactions of NO with aromatic primary amines[a]



Entry	Arylamine	R	Yield of **5** (%)[b]	Recovery of **4** (%)[c]
1	**4a**	4-OMe	77	48
2	**4b**	4-SMe	60	60
3	**4c**	4-Me	66	56
4	**4d**	3-Me	74	61
5	**4e**	2-Me	—	89
6	**4f**	3,5-di-Me	61	72
7	**4g**	2,3-di-Me	—	90
8	**4h**	4-Et	69	71
9	**4i**	4-*i*-Pr	57	79
10	**4j**	H	—	89
11	**4k**	4-Cl	—	90
12	**4l**	4-CN	—	91
13	**4m**	4-NO_2	—	90
14	**4n**	3-NO_2	—	88

[a] All reactions were run with 1.04 mol% TiO_2 (according to the optimized catalyst loading for the NONOates' preparation). [b] Yield of the isolated product based on the reacted arylamines. [c] Yield of the isolated product (see the ESI†).

It is obvious that nanometre-sized TiO_2 does catalyze the reactions of NO with five- or six-membered cyclic amines. Compared to the reported methods,[4] this novel approach has several advantages, such as higher yields, more convenient operation at RT under atmospheric pressure and a more economical application for the large scale preparation of NONOates.

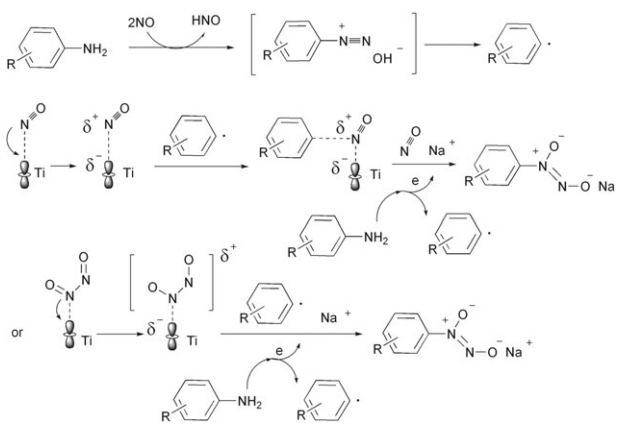
Next, we extended this approach to aromatic amines for the preparation of their corresponding NONOates. Surprisingly, cupferron sodium salts were obtained from arylamines bearing electron donating *para*- and/or *meta*-substituent(s) on the benzene ring (Table 2, entries 1–4, 6, 8 and 9), instead of the desired NONOates.

The structures of the cupferron sodium salts were established by ^{1}H NMR and elemental analysis (see the ESI†). The geometry of N=N double bond in **5** was identified by single crystal X-ray diffraction analysis (see representative compound **6a** (CCDC 705769†), an O^2-methylated derivative of **5a**).

Actually, many attempts have been made to synthesize NONOates through the reaction of NO with primary arylamines, but differing results have been obtained. Drago and Karstetter reacted NO with aniline at RT under high pressure, or at −78 °C under atmospheric pressure, but didn't obtain any of the desired NONOate,[7b] whereas Keefer's group obtained NONOate ammonium salts from the reactions of NO with substituted anilines after 24 h at −78 °C under high pressure.[11] Interestingly, in our case, cupferron sodium salts were formed in the presence of MeONa and nanometre-sized TiO_2 after 48 h at RT under atmospheric pressure.

One question that has arisen is why cupferrons were obtained instead of NONOates. Ohsawa and co-workers reported that the reactions of NO with aromatic primary amines at RT under atmospheric pressure in THF resulted in the corresponding deaminated product *via* an aryl radical mechanism.[12] The differences in our reaction conditions lay in using MeONa as a base and nanometre-sized TiO_2 as a catalyst. As a matter of fact, when **4a** was used as the substrate to conduct the reaction under the same conditions as those in Table 1, using benzene as the solvent, 4-methoxybiphenyl was obtained as a side product in a 6.3% yield, indicating that it was formed *via* an intermediate 4-methoxyphenyl radical, probably derived from phenyl diazonium salts.[12] Therefore, it is likely that the attack of an aryl radical on the NO led to the cupferrons. Noticeably, without TiO_2, cupferron **5a** could not be isolated from the reaction. Thus, we suggest that an aryl radical electron donor could react with NO to form a cupferron, probably under the following conditions and processes. Firstly, nanometre-sized TiO_2 induces a δ^+ charge on the N atom of NO or N_2O_2; secondly, *para*- or *meta*-substituted electron donating groups have a certain ability to enhance the electron density of the aryl radical; thirdly, no electron withdrawing groups and/or sterically hindered *ortho*-substituents exist; last but not least, the aryl radical could initially react with NO to form an intermediate, which might subsequently react with another NO molecule and gain an electron from the arylamine-containing reaction medium, finally generating the cupferron. This probably induces the generation of aryl free radicals starting from arylamine in the reaction mixture to react with NO again. The proposed mechanism is depicted in Scheme 2.

To the best of our knowledge, we are the first to report the nanometre-sized TiO_2-catalyzed reactions of NO with aromatic primary amines in one step to form cupferron sodium salts, and cupferron ammonium salts are usually synthesized by the nitrosation of *N*-hydroxyphenylamines produced by the reduction of the corresponding nitrobenzenes.[13] As important NO donors, cupferrons are able to release NO upon enzymatic, electrochemical, as well as chemical oxidation and their metabolic products are reportedly non-carcinogenic after NO release *in vivo*.[14] Further studies are warranted to improve the yields of cupferrons and investigate their pharmacological applications.



Scheme 2 The proposed mechanisms for nanometre-sized TiO_2-catalyzed reactions of NO with aromatic primary amines.

In conclusion, we have developed a novel nanometre-sized TiO_2-catalyzed preparation of NONOates and cupferrons through the reactions of NO gas with the corresponding amines at RT under atmospheric pressure. The corresponding mechanisms have also been proposed. Importantly, our investigations might not only expand the fields of NO gas involving reactions such as the free radical reactions of NO with alkene or alkyne, but also promote the studies on targeting of NO donor drugs. Further investigations into the applications of this novel method are under way and the results will be reported in due course.

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