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Nitrous oxide as diazo transfer reagent: the synthesis of triazolopyridines

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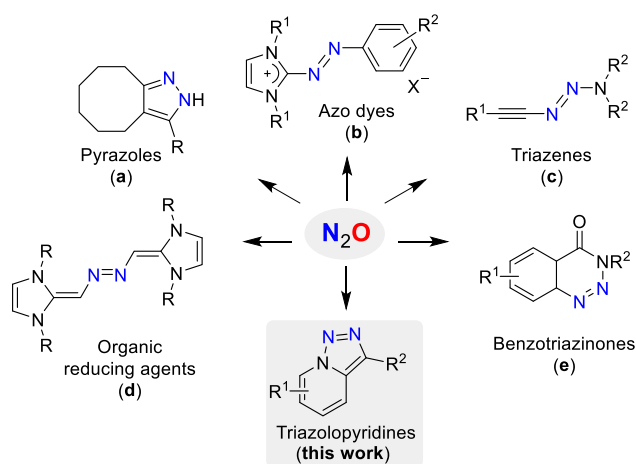
Nitrous oxide is a potential diazo transfer reagent, but applications in organic chemistry are scarce. Here, we show that triazolopyridines and triazoloquinolines are formed in reactions of metallated 2-alkylpyridines or 2-alkylquinolines with N_2O. The reactions can be performed under mild conditions and give synthetically interesting triazoles in moderate to good yields.

Nitrous oxide is well known for its physiological effects ('laughing gas')[1] and for its negative environmental impact (greenhouse gas, ozone depleting).[2] The influence of nitrous oxide on the environment is augmented by the inert character of this gas, which leads to a long persistence time of over 100 years.[3] Notwithstanding its chemical inertness, N_2O is an interesting reagent for synthetic chemistry.[4] It is primarily being used as oxygen atom donor. Applications include the oxidation of olefins to ketones (performed on industrial scale),[5,6] and the selective oxidation of low valent main group[7] and transition metal compounds.[8] Important progress has also been made in the utilization of N_2O as an oxidant in homogeneous, transition metal-catalyzed reactions.[9] In contrast, there are few reactions, in which N_2O serves as a source of nitrogen. A notable example is the synthesis of sodium azide from $NaNH_2$ and N_2O. This reaction was discovered by Wislicenus in 1892,[10] and it allows preparing NaN_3 on large scale.[11] Following this seminal discovery, several other metallated compounds were investigated for their ability to activate N_2O. Nitrogen containing products were observed for reactions with lithium-,[12] sodium-,[13] magnesium-,[14] and calcium-organic compounds,[15] but the transformations were often found to be non-selective, poor-yielding, and/or of limited scope. Synthetically interesting diazo transfer reactions with N_2O have only emerged recently. The reaction of cyclooctynes with N_2O in the presence of alcohols or amines was found to give substituted pyrazoles (Scheme 1a).[16] We have shown that azoimidazolium salts can be prepared from N-heterocyclic carbenes, arenes, and N_2O (Scheme 1b).[17] These azo compounds are strongly colored, and they can be used as dyes. Furthermore, they can be transformed into aminyl radicals,[18] and they can serve as precursors for mesoionic carbene ligands.[19] Nitrous oxide can also be used to build triazenes.[20] Notably, it is possible to access 1-alkynyl triazenes (Scheme 1c), which had not been prepared before. These novel alkynes are versatile starting materials for subsequent transformations.[21] Most recently, N_2O was used to prepare novel organic reducing agents based on N-heterocyclic olefins (Scheme 1d),[22] and different benzotriazinones (Scheme 1e).[23] Below, we report a new type of reaction, in which N_2O acts as diazo transfer reagent. This reaction allows preparing triazolopyridines, which represent highly valuable starting materials for heterocycle synthesis.[24]


Scheme 1 Nitrous oxide as diazo transfer reagent in synthetic organic chemistry.

A first report about the activation of N_2O by organolithium compounds was published in 1953 by Beringer, Farr and Sands.[12j] Reactions of alkyllithium compounds were found to

give different nitrogen-containing products (e.g. hydrazones or azines). It was proposed that these transformations involve diazo compounds as intermediates, which can react further with the alkyllithium reagent (Scheme 2a).[12e-j] Diazo compounds, which are directly linked to 2-pyridyl groups, rapidly cyclize to give triazolopyridines.[24] Therefore, we assumed that the reaction of metallated 2-alkylpyridines with N_2O might give triazolopyridines as main reaction products (Scheme 2b).
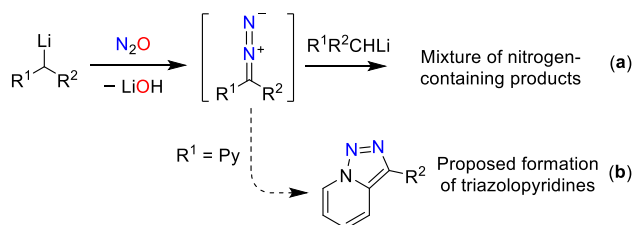
Scheme 2 The reaction of alkyllithium compounds with N_2O gives nitrogen-containing products, and diazo compounds were discussed as putative intermediates (refs. 12e-j) (**a**). Proposed formation of triazolopyridines (**b**).

To test our hypothesis, we lithiated 2-benzylpyridine and subjected it to an atmosphere of N_2O. Analysis of the mixture after a reaction time of 1 h at room temperature showed that triazole **1** had indeed formed. Subsequently, the conditions were optimized (see the Electronic Supplementary Information, ESI). Mild heating at 50 °C for 2 hours in THF (0.05 M) was found to be advantageous for the diazo transfer reaction. A cleaner reaction was observed when the lithiation step was performed in diethyl ether, followed by a solvent switch to THF for the reaction with N_2O. Under these conditions, triazole **1** could be isolated in 82% yield (Scheme 3).

The scope of the diazo transfer reaction was examined next. Chloro (**2**) and methyl substituents (**3**) on the phenyl ring were well-tolerated, whereas electron donating OMe (**4**) and $N(Me)_2$ substituents (**5**) gave lower yields. Apparently, side-reactions take place when the phenyl ring is too strongly activated. Changing the pyridine moiety to lutidine (**6**) and quinoline (**7** and **8**) resulted in good yields. Finally, replacing the phenyl group with 2-pyridyl or 5-indolyl provided the desired products **9** and **10** in moderate yields. It is worth noting that the anion in lithiated bis(2-pyridyl)methane (the precursor of **9**) is highly delocalized, with Li^+ coordinating to both pyridyl groups.[25] The delocalization is expected to lower the nucleophilicity of the organolithium compound, hampering the reaction with N_2O. We have also examined reaction of pyridines with simple alkyl instead of benzyl substituents. A complex mixture of products was observed, and further analyses were not performed.

Stenzel and Klumpp had reported that reactions of *trans*-1,2-di(2-pyridyl)ethylene with organolithium reagents give stable 2-alkylpyridine anions, which can be trapped with electrophiles.[26,27] These results prompted us to explore if we can combine a C–C coupling reaction with the nitrous oxide-induced triazole formation.
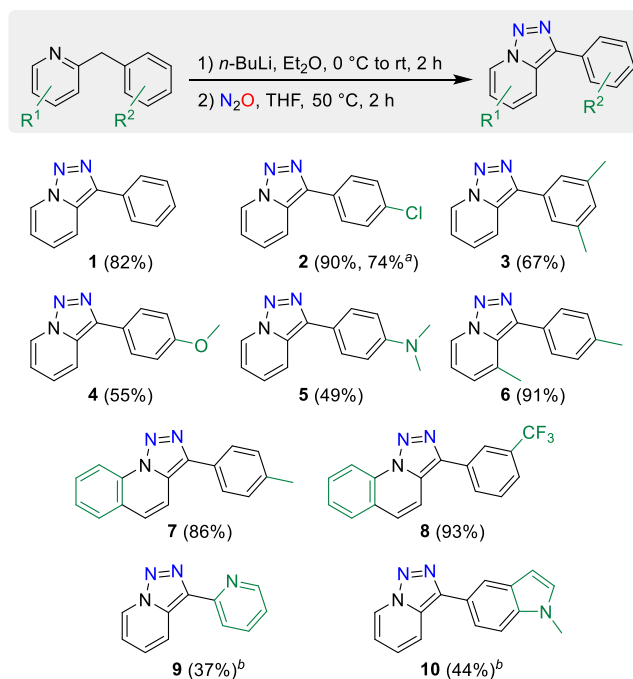
Scheme 3 Synthesis of triazolopyridines and triazoloquinolines with N_2O. The values in brackets refer to isolated yields. *a* Reaction performed on a 5 mmol scale. *b* Extended reaction times for the reaction with N_2O, **9**: 19 h, and **10**: 4 h.

The addition of *n*-BuLi (1.2 equiv) to a solution of *trans*-1,2-di(2-pyridyl)ethylene in THF followed by reaction with N_2O at slightly elevated temperature (50 °C) gave triazolopyridine **11** (Scheme 4). Purification by standard flash chromatography turned out to be difficult. However, by using preparative HPLC, it was possible to isolate **11** in 54% yield. *n*-BuLi could be replaced by *s*-BuLi or *t*-BuLi, giving the triazoles **12** and **13**. Attempts to substitute one of the two pyridyl groups with a phenyl group were met with limited success. 2-Alkenyl quinolines, on the other hand, could be converted into to the triazoles **14** and **15**.
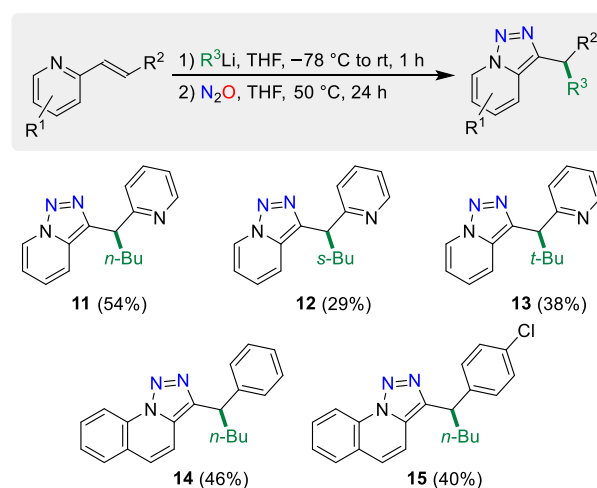
Scheme 4 Synthesis of triazoles by sequential reaction of alkenyl pyridines or quinolines with first organolithium reagents and then N_2O. The values in brackets refer to isolated yields.

Overall, the isolated yields for these sequential C–C, C–N coupling reactions were only modest (29–54%). However, it should be noted that structurally complex triazolopyridines are formed in a simple one-pot procedure.

Triazolopyridines with ester substituents are frequently used as substrates for synthetic transformations.[24] In order to examine if compounds of this kind can be obtained with nitrous oxide, we have investigated the reaction of metallated methyl 2-(pyridine-2-yl)acetate with N_2O. Deprotonation of the ester was achieved by KOtBu.[28] 18-Crown-6 was used as additive to facilitate solubilisation of the metallated pyridine. Subsequent addition of N_2O along with gentle heating resulted in the clean formation of potassium salt **16** (Scheme 5). Acidic work-up gave carboxylic acid **17**, which was isolated in 89% yield. The presence of a carboxylate instead of an ester group in the direct reaction product **16** was evidenced by solution-based analyses (NMR, MS) and by single crystal X-ray diffraction (see ESI). Apparently, the by-product KOH had induced simultaneous hydrolysis of the ester function.[29] The CO_2H group of **17** can be removed by a Ag(I)-catalyzed protodecarboxylation reaction,[30] and details are given in the ESI.
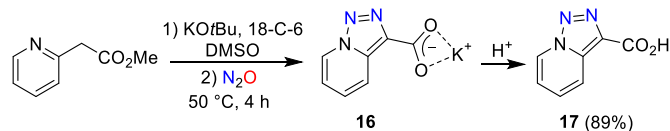
Scheme 5 Synthesis of triazolopyridine **17**.

With regard to the mechanism of the reactions discussed herein, one can propose an initial nucleophilic attack of the carbanion to N_2O to give a diazotate of type **I** (Scheme 6). Elimination of MOH would provide diazo compounds of type **II**, which are prone to cyclize to give the final products. However, it is also conceivable that the nucleophilic attack occurs via the pyridyl N-atom, since metallated 2-alkylpridines display significant charge density at the N-atom.[25,31] In this case, the reaction with N_2O would give aminodiazotates of type **III**. It is worth noting that aminodiazotates have previously been observed in reactions of lithiated amines with N_2O.[20] Elimination of MOH from **III** would give triazolopyridines without involvement of diazo compounds. Attempts to identify intermediates by *in situ* ^{1}H NMR spectroscopy were not successful.
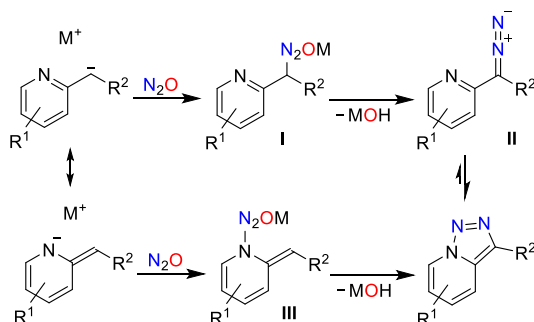
Scheme 6 Proposed mechanism for the synthesis of triazolopyridines from N_2O.

In conclusion, we have shown that nitrous oxide can be used as a diazo transfer reagent for the synthesis of triazolopyridines and triazoloquinolines. The N_2O-based methodology allows accessing synthetically interesting triazoles in moderate to good yields. Traditionally, triazoles with aryl substituents in 3-position (e.g. **1**) are prepared from 2-acylpyridines by condensation with hydrazine followed by oxidation.[32] Alternatively, 2-pyridyl amines can be oxidized with *tert*-butyl nitrite.[33] Our procedure is distinct since it employs 2-alkyl or 2-alkenyl pyridines as starting materials.[34] Furthermore, the compounds are obtained using operationally facile one-pot reactions. More generally, our results are further evidence for the utility of N_2O in synthetic organic chemistry.

Conflicts of interest

There are no conflicts to declare.

Author contributions

I.R.L. and K.S. designed the experiments, I.R.L. performed the experiments and analyzed the data, F.F.-T. collected and processed the X-ray data, and I.R.L. and K.S. co-wrote the manuscript. All authors discussed the results and commented on the manuscript.

Acknowledgements

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Graphic for the TOC:
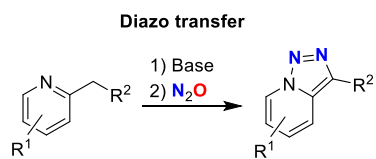
Nitrous oxide (N$_2$O, 'laughing gas') can be used as diazo transfer reagent for the synthesis of triazolopyridines.