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# C–N Bond Formation by the Oxidative Alkylamination of Azines: Comparison of $AgPy_2MnO_4$ versus $KMnO_4$ as Oxidant

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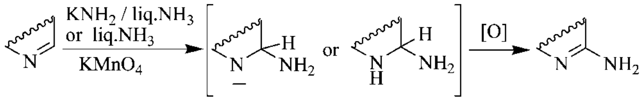
**Keywords:** Nucleophilic substitution / Aromatic substitution / Oxidation / Amination / Density functional theory

Reports on the successful oxidative alkylamination of azines by the $S_N^H$-reaction, with the use of alkylamines other than methylamine, are very scarce. Hitherto, the experimental limitation to extend oxidative amination of azines with $NH_3$/$KMnO_4$ to oxidative alkylamination is solely ascribed to the low solubility of $KMnO_4$ in alkylamines and the increased sensitivity of alkylamines towards oxidation in comparison with ammonia. Our experimental data for the first time prove that there is also a substrate dependence in this type of reaction. 2-Alkylamino-5-nitropyridines and 4-alkylaminoquinazolines were smoothly obtained by the treatment of 3-nitropyridine and quinazoline, respectively, with alkylamine/$AgPy_2MnO_4$. Although $KMnO_4$ still gives moderate to good results with 3-nitropyridine, it is completely useless for reactions with quinazoline with the same alkylamines. The use of $AgPy_2MnO_4$ was found to give equal or superior results to those of $KMnO_4$ depending on the alkylamine and the substrate used and therefore seems to be a promising general oxidant for successful oxidative alkylaminations.

## Introduction

Nucleophilic aromatic substitution of hydrogen ($S_N^H$) is an advanced field of organic chemistry.[1] This methodology does not require any preliminary introduction of a good leaving group into the aromatic or heteroaromatic substrate, and therefore, this method has an important advantage over nucleophilic *ipso*-substitution. Modern $S_N^H$-procedures permit the replacement of hydrogen by C-, N-, O-, S-, Hal-, and P-nucleophiles under surprisingly mild reaction conditions. Oxidative amination of azines with $KNH_2$/$NH_3$/$KMnO_4$ or $NH_3$/$KMnO_4$ (Scheme 1), introduced by van der Plas, is one of the pioneering $S_N^H$-protocols, which has found numerous synthetic applications.[1a,1f] Today, it is a relatively well-explored process. The corresponding oxidative alkylamination of azines with alkylamine/$KMnO_4$ has received only little attention. The majority of the limited number of published examples on oxidative alkylaminations deal with methylamination.[1f,2a–2f] Reports on the use of other alkylamines are surprisingly scarce.[2g–2k] There are two plausible reasons for this. $KMnO_4$, the standard oxidant for oxidative amination, is substantially less soluble or completely insoluble in alkylamines, which probably limits the successful extension of $S_N^H$-amination to $S_N^H$-alkylamination. In addition, alkylamines themselves, especially secondary ones, are more sensitive towards oxidation than ammonia.



Scheme 1. Oxidative amination of azines.

Earlier, the Rostov research team discovered that $AgPy_2MnO_4$ can be used for the alkylamination of very specific bicyclic substrates (azines condensed with an uracil ring).[3] This silver complex is soluble in alkylamines (in contrast with $KMnO_4$) and can easily be prepared from $KMnO_4$, $AgNO_3$ and pyridine.[4] In this paper we describe that $AgPy_2MnO_4$ can serve as a general oxidant to perform alkylamination of simple (but important) heteroaromatic substrates such as 3-nitropyridine and quinazoline under very mild reaction conditions. Equal or superior results were obtained with $AgPy_2MnO_4$ in comparison with those of $KMnO_4$. Moreover, in a lot of cases simply no reaction product could be obtained with $KMnO_4$! The developed oxidative alkylamination procedure is very useful because alkylamino derivatives of these heteroaromatic skeletons represent an essential subunit of a wide variety of biologically active compounds and they find numerous applications in organic, inorganic and organometallic chemistry.[5]

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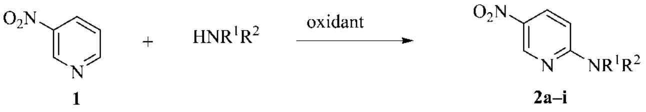
## Results and Discussion

### Experimental Results for the Oxidative Alkylamination of 3-Nitropyridine and Quinazoline

There are only three published examples that deal with the oxidative alkylamination of 3-nitropyridine. In all cases, $KMnO_4$ was used as the oxidant in alkylamine ($MeNH_2$ or $BuNH_2$) as the solvent or in a mixture of alkylamine and a cosolvent ($Et_2NH$/DMSO).[2f,2g] The former procedure yields 6-methylamino-3-nitropyridine in 65% and 6-butylamino-3-nitropyridine in 92% yield. The latter protocol provides 6-diethylamino-3-nitropyridine in 60% yield after a complicated workup due to the cosolvent. We found that the effectiveness of alkylamination of 3-nitropyridine (**1**) in alkylamine (solvent and nucleophile) with the use of $KMnO_4$ as the oxidant seriously depends on the nature of the alkylamine (Scheme 2; Table 1, Entries 1–9). For instance, reaction of **1** with isopropylamine in the presence of 2 equiv. of $KMnO_4$ (8–10 °C, 30 min, then room temp., 2 h) affords 6-isopropylamino-3-nitropyridine (**2a**) in a very high yield (91%) (Table 1, Entry 1), whereas amination with pyrrolidine gives a much lower yield (50%) (Table 1, Entry 5) and the use of benzylamine, homopiperidine or diethylamine doesn't give any reaction product (Table 1, Entries 4, 8 and 9). Treatment of **1** with various primary or secondary alkylamines in the presence of 2 equiv. of $AgPy_2MnO_4$ (8–10 °C, 30 min) yields 6-alkylamino-3-nitropyridines **2a**–**h** in 64–99% yield (Table 1, Entries 10–17). When primary alkylamines are used, 2,6- and 4,6-dialkylamino derivatives are also formed in a small amount. Important to note is that benzylamine and homopiperidine, which do not give reaction products with $KMnO_4$, smoothly convert with our oxidant (Table 1, Entries 13 and 17). In the case of diethylamine, again no reaction is observed with $KMnO_4$ (Table 1, Entry 9), but the yield of **2i** with the use of $AgPy_2MnO_4$ is still disappointing (Table 1, Entry 18). The use of ethanol as a cosolvent did not affect the yield (Table 1, Entry 19).

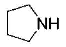
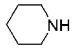
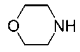
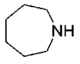
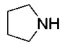
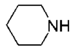
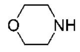
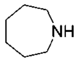
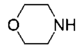


**2**: $NR^1R^2$ = *i*PrNH (**a**), *n*BuNH (**b**), *n*-$C_5H_{11}$NH (**c**), $PhCH_2NH$ (**d**), pyrrolidino (**e**), piperidino (**f**), morpholino (**g**), hexamethyleneimino (**h**), $Et_2N$ (**i**)

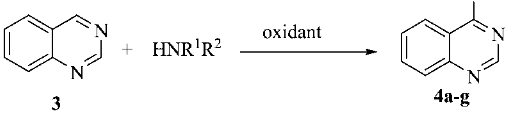
Scheme 2. Synthesis of 6-alkylamino-3-nitropyridines **2**.

Hitherto, there have been no reports on the oxidative alkylamination of quinazoline (**3**). We found that **3** hardly reacts with primary and secondary alkylamines in the presence of $KMnO_4$ (Scheme 3; Table 2, Entries 1–10). In fact, only butylamine gives a practically useful but still low yield of 4-butylaminoquinazoline (Table 2, Entry 2). On the contrary, the use of $AgPy_2MnO_4$ instead of $KMnO_4$ leads to the desired 4-alkylaminoquinazolines (**4a**–**e**, **4g**, **4h**) in good to excellent yields (68–96%) (Table 2, Entries 11–15, 17 and 18). Only alkylamination of **3** with pyrrolidine, homopiper-

Table 1. Oxidative alkylamination of 3-nitropyridine (**1**).

| Entry | $HNR^1R^2$ | Oxidant | Method[a] | Product | Yield [%] |
|---|---|---|---|---|---|
| 1 | *i*-$C_3H_7NH_2$ | $KMnO_4$ | *A* | **2a** | 91 |
| 2 | *n*-$C_4H_9NH_2$ | $KMnO_4$ | *A* | **2b** | 93 |
| 3 | *n*-$C_5H_{11}NH_2$ | $KMnO_4$ | *A* | **2c** | 82[b] |
| 4 | $C_6H_5CH_2NH_2$ | $KMnO_4$ | *A* | **2d** | 0 |
| 5 |  | $KMnO_4$ | *A* | **2e** | 50 |
| 6 |  | $KMnO_4$ | *A* | **2f** | 70 |
| 7 |  | $KMnO_4$ | *A* | **2g** | 71 |
| 8 |  | $KMnO_4$ | *A* | **2h** | 0 |
| 9 | $(C_2H_5)_2NH$ | $KMnO_4$ | *A*[c] | **2i** | 0 |
| 10 | *i*-$C_3H_7NH_2$ | $AgPy_2MnO_4$ | *B* | **2a** | 83[d] |
| 11 | *n*-$C_4H_9NH_2$ | $AgPy_2MnO_4$ | *B* | **2b** | 91[e] |
| 12 | *n*-$C_5H_{11}NH_2$ | $AgPy_2MnO_4$ | *B* | **2c** | 91[f] |
| 13 | $C_6H_5CH_2NH_2$ | $AgPy_2MnO_4$ | *B* | **2d** | 64[g] |
| 14 |  | $AgPy_2MnO_4$ | *B* | **2e** | 99 |
| 15 |  | $AgPy_2MnO_4$ | *B* | **2f** | 98 |
| 16 |  | $AgPy_2MnO_4$ | *B* | **2g** | 96 |
| 17 |  | $AgPy_2MnO_4$ | *B* | **2h** | 82 |
| 18 | $(C_2H_5)_2NH$ | $AgPy_2MnO_4$ | *B* | **2i** | 14 |
| 19 | $(C_2H_5)_2NH$ | $AgPy_2MnO_4$ | *D* | **2i** | 20 |
| 20 | *i*-$C_3H_7NH_2$ | CAN | *C* | **2a** | 22[h] |
| 21 |  | CAN | *C* | **2g** | 15 |
| 22 | $(C_2H_5)_2NH$ | $AgMnO_4$ | *E* | **2i** | 9 |

[a] *A*: 8–10 °C, 30 min, then room temp., 2 h; *B*: 8–10 °C, 30 min; *C*: 8–10 °C, 30 min, then room temp., 24 h; *D*: reaction was carried out in $Et_2NH$/EtOH (1:1) at –10 to –3 °C, 1.5 h; *E*: 8–10 °C, 30 min. [b] 2,6- and 4,6-Bis(amylamino)-3-nitropyridine were also obtained in 1.2% total yield. [c] Reaction doesn't proceed at room temp. or heated at reflux for 24 h. [d] 2,6- and 4,6-Bis(isopropylamino)-3-nitropyridine were also obtained in 10% total yield. [e] 2,6- and 4,6-Bis(butylamino)-3-nitropyridine were also obtained in 2% total yield. [f] 2,6- and 4,6-Bis(amylamino)-3-nitropyridine were also obtained in 3.6% total yield. [g] 2,6- and 4,6-Bis(benzylamino)-3-nitropyridine were also obtained in 3% total yield. [h] 2,6- and 4,6-Bis(isopropylamino)-3-nitropyridine were also obtained in 2% total yield.

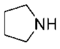
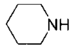
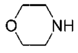
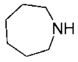
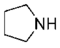
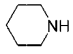
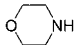
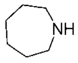


**4**: $NR^1R^2$ = *i*PrNH (**a**), *n*BuNH (**b**), *n*-$C_5H_{11}$NH (**c**), *c*-$C_6H_{11}$NH (**d**), $PhCH_2NH$ (**e**), pyrrolidino (**f**), piperidino (**g**), morpholino (**h**), hexamethyleneimino (**i**), $Et_2N$ (**j**)

Scheme 3. Synthesis of 4-alkylaminoquinazolines **4**.

dine and diethylamine provides lower yields of corresponding 4-alkylamino derivatives **4f**, **4i** and **4j**, respectively (Table 2, Entries 16, 19 and 20).

Table 2. Oxidative alkylamination of quinazoline (**3**).

| Entry | $HNR^1R^2$ | Oxidant | Method[a] | Product | Yield [%] |
|---|---|---|---|---|---|
| 1 | *i*-$C_3H_7NH_2$ | $KMnO_4$ | *A* | **4a** | 8 |
| 2 | *n*-$C_4H_9NH_2$ | $KMnO_4$ | *A* | **4b** | 39 |
| 3 | *n*-$C_5H_{11}NH_2$ | $KMnO_4$ | *A* | **4c** | 6 |
| 4 | *c*-$C_6H_{11}NH_2$ | $KMnO_4$ | *A* | **4d** | 5 |
| 5 | $C_6H_5CH_2NH_2$ | $KMnO_4$ | *A* | **4e** | 0 |
| 6 |  | $KMnO_4$ | *A* | **4f** | trace |
| 7 |  | $KMnO_4$ | *A* | **4g** | trace |
| 8 |  | $KMnO_4$ | *A* | **4h** | 2 |
| 9 |  | $KMnO_4$ | *A* | **4i** | 0 |
| 10 | $(C_2H_5)_2NH$ | $KMnO_4$ | *A* | **4j** | 0 |
| 11 | *i*-$C_3H_7NH_2$ | $AgPy_2MnO_4$ | *B* | **4a** | 86 |
| 12 | *n*-$C_4H_9NH_2$ | $AgPy_2MnO_4$ | *B* | **4b** | 93 |
| 13 | *n*-$C_5H_{11}NH_2$ | $AgPy_2MnO_4$ | *B* | **4c** | 96 |
| 14 | *c*-$C_6H_{11}NH_2$ | $AgPy_2MnO_4$ | *B* | **4d** | 87 |
| 15 | $C_6H_5CH_2NH_2$ | $AgPy_2MnO_4$ | *C* | **4e** | 91 |
| 16 |  | $AgPy_2MnO_4$ | *C* | **4f** | 31 |
| 17 |  | $AgPy_2MnO_4$ | *C* | **4g** | 68 |
| 18 |  | $AgPy_2MnO_4$ | *C* | **4h** | 96 |
| 19 |  | $AgPy_2MnO_4$ | *C* | **4i** | 32 |
| 20 | $(C_2H_5)_2NH$ | $AgPy_2MnO_4$ | *C* | **4j** | 28 |
| 21 | *n*-$C_4H_9NH_2$ | $AgMnO_4$ | *D* | **4b** | 81 |
| 22 | $C_6H_5CH_2NH_2$ | $AgMnO_4$ | *D* | **4e** | 78 |

[a] *A*: 8–10 °C, 30 min, then room temp., overnight; *B*: 8–10 °C, 30 min; *C*: 8–10 °C, 1 h; *D*: 8–10 °C, 1 h.

Although $AgPy_2MnO_4$ can easily be prepared in one step, we also briefly checked the ability of commercially available $AgMnO_4$ to serve as an oxidant in the oxidative alkylamination of **1** and **3**. We supposed that the silver ion of this permanganate salt can form complexes with alkylamines in situ [e.g. $Ag(alkylamine)_2MnO_4$] and in this way a gradual dissolving in alkylamines should be achieved. This assumption proved to be right because we visually observed a smooth dissolving of the silver salt in alkylamines with the formation of a purple-coloured solution. As test cases for our concept, the reactions of quinazoline **3** with butylamine and benzylamine in the presence of $AgMnO_4$ were attempted. The corresponding 4-alkylaminoquinazolines **4b** and **4e** were obtained in 81% and 78% yield, respectively (Table 2, Entries 21 and 22). Unfortunately, there is a slight reduction in the obtained yields (12% for **4b** and 13% for **4e**) in comparison with $AgPy_2MnO_4$ as the oxidant. $AgMnO_4$ even worked in the case of a problematic amine such as diethylamine, but again, a similar reduction in the yield is observed (Table 1, Entry 22).

We also attempted to search for other alternative oxidants to $AgPy_2MnO_4$ that would be appropriate for alkylamination. Commercially available cerium(IV) ammonium nitrate, which has already been applied for the oxidation of some $\sigma^H$ adducts,[6] was substantially less effective as the oxidant in the reaction of **1** with isopropylamine and morpholine (Table 1, Entries 20 and 21). Addition of THF as a cosolvent to the former reaction had a negative effect and affords compound **2a** in a lower yield (11%).

From the experimental data it can be concluded that: 1) Oxidative alkylamination of both **1** and **3** proceeds regioselectively. 2) There is a huge difference between the oxidative alkylamination of **1** and **3**: the alkylamination of **1** with the use of either $KMnO_4$ or $AgPy_2MnO_4$ as the oxidant, gives moderate to good yields of 6-alkylamino-3-nitropyridines, whereas in the case of **3**, only $AgPy_2MnO_4$ can be used to prepare 4-alkylaminoquinazolines. In order to try to rationalize these observed differences with $KMnO_4$ on **1** and **3**, $^1H$ NMR experiments and DFT (density functional theory) calculations on $\sigma^H$ adduct formation have been performed. The regioselectivity was investigated by two different theoretical approaches (Fukui function and FMO theory).

## Regioselectivity for the $S_N^H$-Reactions of 3-Nitropyridine and Quinazoline with Alkylamines

The experimental data in Tables 1 and 2 show that for all $S_N^H$-reactions, the addition of the alkylamine to 3-nitropyridine (**1**) occurs at C-6, whereas for quinazoline (**3**) the addition solely occurs at C-4. We tried to explain these results by calculating and analyzing the spatial distribution of the Fukui function for nucleophilic attack $f^+(r)$ on the substrates.[7] The Fukui function for nucleophilic attack $f^+(r)$ is defined as $f^+(r) = \rho_{N+1}(r) - \rho_N(r)$, where $\rho_N(r)$ is the electron density at a point $r$ in space around the molecule, $N$ corresponds to the number of electrons in the neutral molecule and $N+1$ refers to the number of electrons in the corresponding radical anion (obtained by adding an electron to the LUMO of the neutral molecule). The Fukui functions for nucleophilic attack $f^+(r)$ obtained for the B3LYP/6-31G(d) equilibrium geometries of **1** and **3** are shown in Figure 1. It can be clearly seen that for 3-nitropyridine (**1**), the maximum of the Fukui function $f^+(r)$ is localized on C-6, whereas for quinazoline (**3**), $f^+(r)$ reaches a maximum at C-4. It should be noted that the data in Figure 1 illustrate that for both 3-nitropyridine and quinazoline, secondary maxima appear at other carbon atoms in the Fukui function, at C-2 and C-4, and at C-5, C-7, and C-8, respectively. The values for the Fukui function at C-5, C-7 and C-8 obtained for quinazoline are significantly lower than that obtained for C-4. Hence, for C-5, C-7 and C-8, no addition is expected and observed. The values for C-2 and C-4 obtained for 3-nitropyridine are larger than those for C-5, C-7 and C-8 in quinazoline. This is in agreement with the formation of small amounts of 2,6- and 4,6-dialkylamino-3-nitropyridines as observed in our experiments and earlier reported data[1f] on the oxidative amination of 3-nitropyridine in liquid ammonia, where a mixture of 2-, 4- and 6-amino-3-nitropyridine is obtained.[9] Thus, for both substrates, the spatial distribution of the Fukui functions and the position of the maxima are in excellent agreement with the experimental observations reported and consequently show that the Fukui function, although hitherto never used for that purpose, is able to correctly predict the regioselectivity of oxidative alkylaminations.

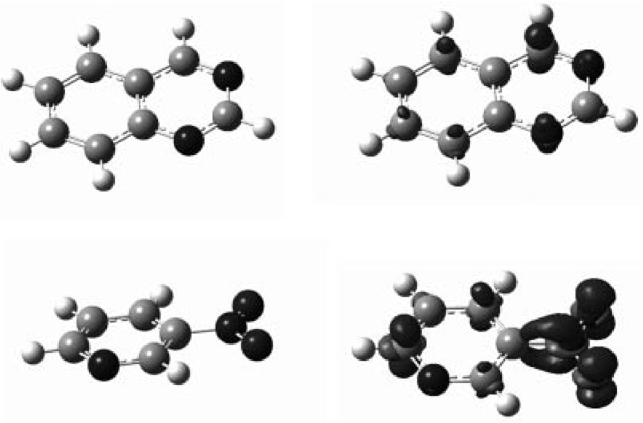


Figure 1. B3LYP/6-31G(d) equilibrium geometries (left) and the corresponding Fukui function (right) for nucleophilic attack on quinazoline (**3**) (top) and 3-nitropyridine (**1**) (bottom). The values for the isodensity surfaces were set to 0.0105 $e\ a_o^{-3}$ and 0.075 $e\ a_o^{-3}$, respectively.

We also compared the results that were based on Fukui functions with classical theoretical approaches in which the regioselectivity, with the nucleophile taken into account, is predicted with the use of Frontier Molecular Orbital Theory (FMO).[8] In FMO theory, the reaction between an organic substrate *A* and a nucleophile *N* is described with the use of second order perturbation theory. This model states that when substrate *A* has several potential reaction centres, the nucleophile *N* will most favourably attack the position that leads to the highest stabilization energy. The latter, in a first approximation, can be estimated by the expressions

$$\Delta E \approx 2\left[\frac{C_s^2(LUMO)}{E^n_{HOMO}-E^a_{LUMO}}\right] \qquad \text{or}$$

$$\Delta E \approx 2\left[\frac{C_s^2(LUMO)}{E^n_{HOMO}-E^a_{LUMO}}+\frac{C_s^2(LUMO+1)}{E^n_{HOMO}-E^a_{LUMO+1}}\right]$$

in which $C_S(LUMO)$ and $C_S(LUMO+1)$ refer to the coefficients obtained from the LCAO analysis, $E^n_{HOMO}$, $E^a_{LUMO}$and $E^a_{LUMO+1}$ are the energies of the HOMO orbital in *N* and the LUMO and LUMO+1 orbitals in *A*, respectively. The first equation is used for cases when the energy difference between LUMO and LUMO+1 is large and only the mixing of the HOMO orbital of *N* and the LUMO orbital of *A* should be taken into account. For these cases, the value for the term $C_S^2(LUMO+1)/E^n_{HOMO} - E^a_{LUMO+1}$ is small and, therefore, negligible. The second equation is required if the energy difference $E^n_{HOMO} - E^a_{LUMO+1}$ is small and mixing occurs between the HOMO orbital of *N* and both the LUMO and the LUMO+1 orbitals of *A*. Interestingly, the calculated values of $\Delta E$ show that for both **1** and **3**, the regioselectivity is correctly predicted if only the LUMO orbital of *A* is taken into account. However, when the correction for LUMO+1 (of which the value can not be neglected in our case) is added, the predicted regioselectivity is incorrect (C-4 for 3-nitropyridine and C-2 for quinazoline).

## DFT Reaction Profiles for $\sigma^H$ Adduct Formation of 3-Nitropyridine and Quinazoline with Alkylamines

Mechanistically, an oxidative alkylamination consists of $\sigma^H$ adduct formation followed by oxidation (aromatization).[1a,1f] In order to try to rationalize the experimental observations, we decided to gain theoretical data on the relative stability of the $\sigma^H$ adducts with respect to the substrates. Theoretical information for the $\sigma^H$ adducts of 3-nitropyridine (**1**) and quinazoline (**3**) with three model alkylamines (diethylamine, pyrrolidine and butylamine) was obtained by carrying out density functional calculations at the B3LYP/6-31G(d) level. For both the substrates and adducts, geometry optimizations were performed with the use of tight convergence criteria. In addition, for all species, the vibrational frequencies were derived by calculating the standard harmonic force fields. The equilibrium structures obtained for the $\sigma^H$ adducts are shown in Figure 2. The differences in the internal energy $\Delta E_r$ (obtained by comparing the calculated energies of the starting materials and the $\sigma^H$ adducts), the corresponding values for $\Delta H^o_r$ and $\Delta G^o_r$ (derived by applying standard statistical thermodynamics) and the values for the equilibrium constants are summarized in Table 3. Additional information on the reaction profile was obtained by localizing the characteristic transition states. These were obtained by adopting the synchronous transit-guided quasi-Newton method developed by H. B. Schlegel and coworkers (Figure 3).[10] The values for the activation energies, obtained by comparing the calculated energies of the substrates and those of the transition states, are also given in Table 3. For all species, the formation of an $\sigma^H$ adduct involves a transfer from a hydrogen atom localized in the amine towards the ring nitrogen atom next to the interacting carbon atom. Of course, in reality this transfer can be done by the aid of the alkylamine solvent, but this is not incorporated in our gas phase calculations. The activation energies obtained for the different species vary from 157.9 to 185.3 kJ·mol$^{-1}$; the values for diethylamine are significantly larger than those obtained for pyrrolidine and butylamine. The differences in the activation energies can be rationalized as the result of a combination of two competing factors: the difference in steric hindrance [due to the overlap of the alkylamine side chain(s) with the delocalized π-system] and the difference in electron donating properties of primary and secondary alkylamines.

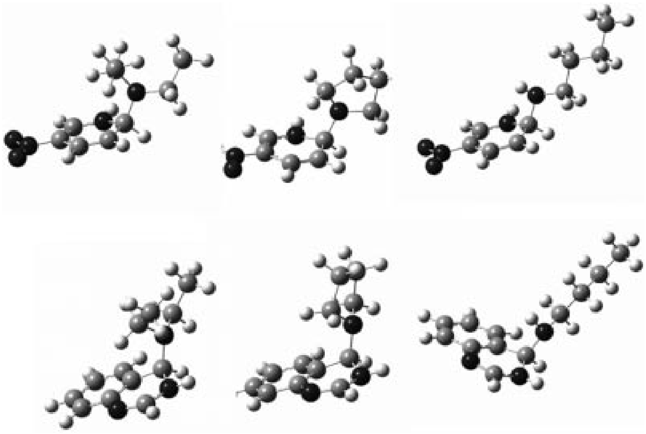


Figure 2. B3LYP/6-31G(d) equilibrium geometries for the different $\sigma^H$ adducts of 3-nitropyridine (**1**) (top) and quinazoline (**3**) (bottom) with diethylamine, pyrrolidine and butylamine.

Table 3. B3LYP/6-31G(d) thermodynamic properties and activation energies, in kJ·mol$^{-1}$, derived for the $\sigma^H$ adducts of 3-nitropyridine (**1**) and quinazoline (**3**) with butylamine, pyrrolidine and diethylamine (in the gas phase).

| Substrate | Amine | $\Delta E_r$ | $\Delta H_r^o$ | $\Delta G_r^o$ | $K_{eq}$ | $E_a$ |
|---|---|---|---|---|---|---|
| Quinazoline (**3**) | butylamine | –3.4 | 6.4 | 58.4 | $4.1 \cdot 10^{-11}$ | 161.4 |
| | pyrrolidine | –2.7 | 6.1 | 59.5 | $2.6 \cdot 10^{-11}$ | 157.9 |
| | diethylamine | 18.2 | 27.0 | 81.1 | $3.8 \cdot 10^{-15}$ | 177.0 |
| 3-Nitropyridine (**1**) | butylamine | 23.0 | 32.5 | 83.6 | $1.4 \cdot 10^{-15}$ | 177.7 |
| | pyrrolidine | 23.5 | 31.7 | 83.9 | $1.2 \cdot 10^{-15}$ | 169.8 |
| | diethylamine | 45.1 | 53.8 | 108.2 | $6.0 \cdot 10^{-20}$ | 185.3 |

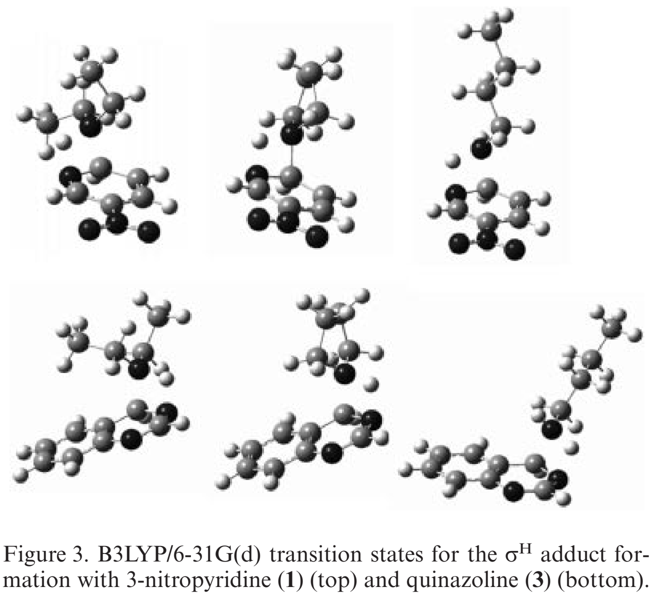


Figure 3. B3LYP/6-31G(d) transition states for the $\sigma^H$ adduct formation with 3-nitropyridine (**1**) (top) and quinazoline (**3**) (bottom).

### $^1$H NMR Measurements for $\sigma^H$ Adduct Formation of 3-Nitropyridine and Quinazoline with Alkylamines

Earlier, several research groups reported that $^1$H NMR spectroscopy is an effective diagnostic tool for the detection of covalent $\sigma^H$ adducts because their formation is characterized by an upfield shift of all proton signals in comparison with the same signals in the substrate.[1a,1f] We therefore tried to record the $^1$H NMR of the $\sigma^H$ adducts of 3-nitropyridine (**1**) and quinazoline (**3**) with the three model alkylamines that were used in our theoretical calculations. Measurement of the $^1$H NMR spectra of **3** in a mixture of butylamine, pyrrolidine or diethylamine and $CDCl_3$ (volume ratio of 3:2) at –30 °C showed that stable C-4 σ adducts are formed with butylamine and pyrrolidine. For diethylamine, no $\sigma^H$ adducts could be observed. Figure 4 shows, as a representative example, the spectrum of a solution of **3** in butylamine/$CDCl_3$ at –30 °C. It can be clearly seen that the spectrum contains two groups of signals: signals with higher intensity at $\delta$ = 6.5–8.3 ppm which correspond to substrate **3** and less intense signals in a more highfield region ($\delta$ = 4.1–6.0 ppm) of the $\sigma^H$ adduct of **3** with butylamine. The same picture was observed for **3** in pyrrolidine and $CDCl_3$ at –30 °C. In both cases, the upfield shift of 4-H is especially considerable ($\Delta\delta$ = 3.8–4.0 ppm) due to the rehybridization of the C-4 atom from sp$^2$ in quinazoline to sp$^3$ in the $\sigma^H$ adduct (Table 4). The value of this shift is in agreement with those reported for $\sigma^H$ adducts of azines with ammonia or methylamine.[1f] Spectra recorded at –30 °C for 30 min after dissolution of the substrate were the same as those obtained immediately after the solution was mixed, whereas an increase in the temperature to 10 °C (the temperature at which the reactions are executed) led to a lower but still significant concentration of the $\sigma^H$ adduct. The $^1$H NMR spectra of solutions of **1** in a mixture of butylamine, pyrrolidine or diethylamine and $CDCl_3$ (volume ratio of 3:2) at –30 °C showed no evidence for the formation of alkylamino-$\sigma^H$ adducts. Because the equilibrium constants ($K_{eq}$) presented in Table 3 were calculated for the gas phase, only their relative magnitudes can be compared with our experimental observations (by taking into account the common nature of the $\sigma^H$ adducts of **1** and **3** with different alkylamines). As can be deduced from Table 3, the $K_{eq}$ are in accordance with the experimental evidence that only the $\sigma^H$ adducts of the addition reaction of quinazoline with butylamine and pyrrolidine are in high enough concentration present to be detected at –30 °C. These two addition reactions have the highest calculated $K_{eq}$ values of the studied set. The $K_{eq}$ for the formation of the other four σ adducts is a factor $10^4$ to $10^9$ smaller, which strongly supports the fact that we did not observe them in the $^1$H NMR spectrum at –30 °C. The observed decrease in the concentration of the $\sigma^H$ adducts of **3** with butylamine and pyrrolidine at 10 °C is in agreement with the calculated temperature dependence of $\Delta G_r^o$ ($\Delta S_r^o$ is negative) (Table 3).

### Rationalization of the Differences Observed in the Oxidative Alkylamination of 3-Nitropyridine and Quinazoline with the Use of $KMnO_4$ and $AgPy_2MnO_4$

As we already mentioned above, when we compare the $S_N^H$-reactions of 3-nitropyridine (**1**) and quinazoline (**3**) with the same alkylamine and $KMnO_4$ as the oxidant, we clearly observe a huge difference. With isopropylamine, butylamine, amylamine, pyrrolidine, piperidine and morpholine good to excellent yields of 6-alkylamino-3-nitropyri-

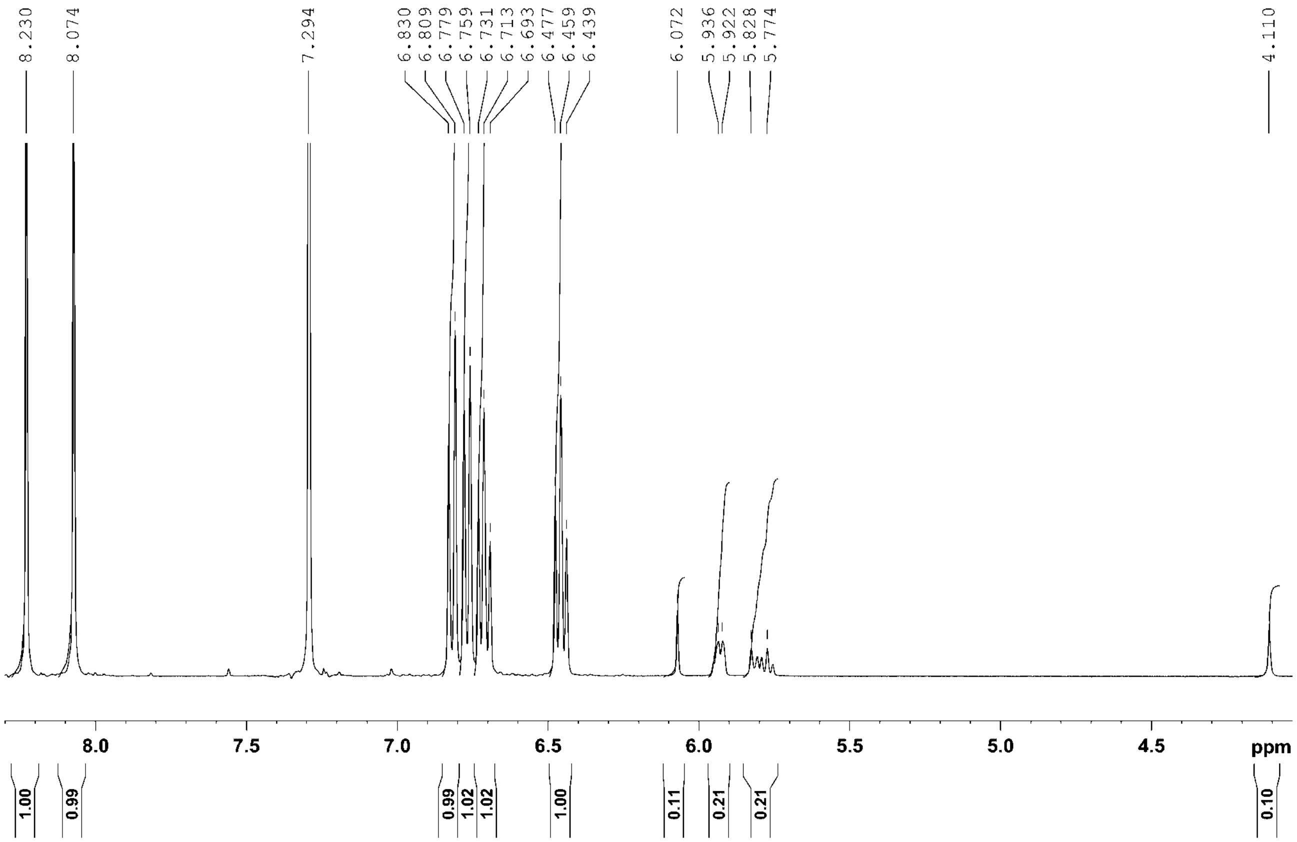


Figure 4. $^1$H NMR spectrum of quinazoline (**3**) in butylamine/CDCl$_3$ (3:2) at –30 °C.

Table 4. $^1$H NMR spectroscopic data of quinazoline (**3**) and its 4-alkylamino $\sigma^H$ adducts (the spectra were measured at –30 °C after 30 min).

| Compound | Solvent | Chemical shifts, $\delta$ [ppm] | | | | | |
|---|---|---|---|---|---|---|---|
| | | 2-H | 4-H | 5-H | 6-H | 7-H | 8-H |
| Quinazoline (**3**) | butylamine/CDCl$_3$, 3:2 | 8.23 | 8.04 | 6.77 | 6.71 | 6.46 | 6.82 |
| $\sigma^H$ Adduct of **3** and butylamine | | 6.07 | 4.11 | 5.92 | 5.83 | 5.77 | 5.93 |
| $\Delta\delta$ | | 2.16 | 3.93 | 0.85 | 0.88 | 0.69 | 0.89 |
| Quinazoline (**3**) | pyrrolidine/CDCl$_3$, 3:2 | 8.22 | 8.04 | 6.78 | 6.71 | 6.46 | 6.81 |
| $\sigma^H$ Adduct of **3** and pyrrolidine | | 6.12 | 4.29 | 5.89 | 5.76 | 5.74 | 5.91 |
| $\Delta\delta$ | | 2.10 | 3.75 | 0.89 | 0.95 | 0.72 | 0.90 |
| Quinazoline (**3**) | homopiperidine/CDCl$_3$, 3:2 | 8.28 | 8.13 | 6.82 | 6.77 | 6.52 | 6.87 |
| $\sigma^H$ Adduct of **3** and homopiperidine | | 6.17 | 4.30 | 5.98 | 5.84 | 5.82 | 5.99 |
| $\Delta\delta$ | | 2.11 | 3.83 | 0.84 | 0.93 | 0.70 | 0.88 |

dine **2a**–**c** and **2e**–**g** can be obtained with KMnO$_4$ (Table 1, Entries 1–3, 5–7), whereas the same alkylamines and oxidant give a very poor conversion of **3** to the corresponding 4-alkylaminoquinazolines **4a**–**c** and **4f**–**h** (Table 2, Entries 1–3, 6–8). When AgPy$_2$MnO$_4$ is used as the oxidant, the $S_N^H$-reactions of **3** with isopropylamine, butylamine, amylamine, pyrrolidine, piperidine and morpholine uniformly give good results. At first glance, this seems rather strange because a mixture of **3** and a primary alkylamine (butylamine) or a secondary cyclic alkylamine (pyrrolidine), in the absence of an oxidant, resulted in a measurable $\sigma^H$ adduct in the $^1$H NMR spectrum, whereas a mixture of **1** and the same alkylamine gave no measurable addition reaction. With the consideration that covalent amination is usually a rapid equilibrium,[1a,1f] our experimental results can be rationalized by a difference in the rate of the oxidation step; the oxidation process must be substantially faster for **1** than for **3**. The overall reaction rate will be determined by the equilibrium constants of the $\sigma^H$ adduct formation, by the rate constants of their oxidation and by the differences in the solubilities of the oxidants. With the low solubility of KMnO$_4$ in alkylamines taken into account, a good result can only be achieved with a substrate whose $\sigma^H$ adducts are oxidized fast. 3-Nitropyridine (**1**) seems to be such a substrate. With the use of AgPy$_2$MnO$_4$, very good solubility is observed, and thus, a higher concentration of permanganate in the alkylamine solvent is obtained. Therefore, this oxidant gives such a huge difference in performance (in comparison with $KMnO_4$) with quinazoline (**3**), where the oxidation step is slower. The possible interference of the silver ion in the oxidation of the $\sigma^H$ adduct by $AgPy_2MnO_4$ has been excluded by an unsuccessful oxidative alkylamination reaction of **3** with butylamine and by using $AgNO_3$ as the oxidant. Secondary cyclic amines (Table 1, Entries 5–7) give lower yields than those of primary amines (Table 1, Entries 1–3) in $S_N^H$-reactions of **1** when $KMnO_4$ is used. However, the yields are improved by using $AgPy_2MnO_4$ (Table 1, Entries 14–16). The basis for this difference lies in the fact that secondary alkylamines are more easily oxidized than primary amines[11] and $KMnO_4$ has a much lower solubility in the former. Therefore, at very low concentrations of permanganate, the competition between $\sigma^H$ adduct and secondary amine oxidation will favour oxidation of the secondary alkylamine and all of the oxidant will be consumed. For the reaction of **1**, as well as **3**, with benzylamine and homopiperidine no reaction products are obtained with $KMnO_4$ (Table 1, Entries 4 and 8; Table 2, Entries 5 and 9). This is most probably simply due to the insolubility of $KMnO_4$ in these alkylamines because the $\sigma^H$ adduct of quinazoline and homopiperidine could be detected by $^1H$ NMR (Table 4). The failure of **1** and **3** to react with diethylamine with the use of $KMnO_4$ as the oxidant (Table 1, Entry 9; Table 2, Entry 10) might also be solely due to the insolubility of the oxidant in diethylamine, but we feel that the impossibility to measure the $\sigma^H$ adduct of **3** with diethylamine by $^1H$ NMR at –30 °C might indicate that in these cases addition of the nucleophile is sterically hampered.

### Comparison of the $S_N^H$-Protocol with Classical Procedures for the Preparation of 6-Alkylamino-3-nitropyridines and 4-Alkylaminoquinazolines

The main synthetic method for the synthesis of 6-alkylamino-3-nitropyridines is by nucleophilic aromatic substitution with a halo,[12a] *N*-alkylnitrosoamino,[12b] *N*-alkylnitroamino,[12c] dihydrooxazol-2-yl[12d] or sulfonate[12e] group as the leaving group in the corresponding 6-X-3-nitropyridine substrate. Similarly, 4-alkylaminoquinazolines are mainly prepared by nucleophilic aromatic substitution of a halo,[13a] phenylthio,[13b] hydroxy,[13c] trichloromethyl[13d] or other specific leaving group on the corresponding 4-X-quinazoline. Other synthetic procedures for the synthesis of 6-alkylamino-3-nitropyridines involve the Diels–Alder reaction of 5-nitropyrimidine with 1,1-bis(dialkylamino)ethenes[12f] and for 4-alkylaminoquinazolines the Dimroth rearrangement of 4-iminoquinazolines[13e] and the thermal ring contraction of 5-alkylamino-3*H*-1,4-benzodiazepines.[13f] It is clear that the oxidative alkylamination with alkylamine/$AgPy_2MnO_4$ has some important advantages over these classical procedures because it is based on stable commercially available substrates. Moreover, the synthetic protocol is experimentally simple and very mild reaction conditions are involved. In addition, the reaction products can be easily isolated and, in general, high yields are obtained. At first glance one might think that $AgPy_2MnO_4$ itself is a very expensive oxidant. However, $AgPy_2MnO_4$ is easily prepared in one step from $AgNO_3$, $KMnO_4$ and pyridine. In comparison with well-known classical mild oxidants such as cerium(IV) ammonium nitrate (CAN)[1g,6] and Dess–Martin periodinane (DMP),[14] which are used in at least equimolar amounts, $AgNO_3$ is actually not so expensive: CAN is only 1.5 times less expensive per mol and DMP is 22 times more expensive.[15]

## Conclusions

6-Alkylamino-3-nitropyridines and 4-alkylaminoquinazolines were smoothly obtained by treatment of 3-nitropyridine and quinazoline, respectively, in alkylamine solvents with $AgPy_2MnO_4$. $AgPy_2MnO_4$ seems to be a general oxidant for successful oxidative alkylaminations. For quinazoline, no successful oxidative alkylaminations had been reported in the literature yet. This is not surprising as we found that $KMnO_4$ (the classical oxidant for oxidative amination) does not work for the corresponding alkylamination. The comparison of the oxidative alkylamination of 3-nitropyridine and quinazoline in the same alkylamines (acting as solvent and nucleophile) with the use of $KMnO_4$ revealed that there is some solubility of this oxidant in most of the alkylamines used. Therefore, another not previously described factor limits the oxidative alkylamination of quinazoline with $KMnO_4$. On the basis of the $^1H$ NMR experiments and DFT calculations, we conclude that there is an important substrate dependence on the reaction and that the rate of the oxidation of the intermediate alkylamino adduct plays a key role.

## Experimental Section

All melting points were determined with a Büchi apparatus and are uncorrected. The $^1H$- and $^{13}C$ NMR spectra were recorded with a Bruker spectrometer Avance 400 in the solvent indicated with TMS as an internal standard. All coupling constants are given in Hertz and chemical shifts are given in parts per million. 3-Nitropyridine (ABCR GmbH & Co.), quinazoline (ABCR GmbH & Co.) and all alkylamines (Acros and Aldrich) were obtained from commercial sources and used as such. Flash column chromatography was performed with Kieselgel 60 (ROCC, 0.040–0.063 mm). Density functional calculations were performed with the use of Gaussian03/TCP Linda[16] as implemented on the CalcUA supercomputing cluster. To avoid confusion in the regioselectivity of the oxidative alkylaminations of 3-nitropyridine, only in the abstract and the Experimental Section the numbering for the reaction products was based on IUPAC nomenclature.

**General Procedure for the Oxidative Alkylamination of 3-Nitropyridine (1):** To a stirred solution of 3-nitropyridine (**1**) (0.124 g, 1 mmol) in the appropriate alkylamine (10 mL) at 8–10 °C, $AgPy_2MnO_4$ (0.770 g, 2 mmol) was added in small portions over a 30 min period. The excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was grinded with silica gel (3–4 g), brought onto a column with silica gel (3.5 × 30 cm) and purified by flash column chromatography with dichloromethane as the eluent to yield 2-alkylamino-5-nitropyridine (**2**).

Reactions with $KMnO_4$ (0.316 g, 2 mmol), CAN (1.096 g, 2 mmol) or $AgMnO_4$ (0.454 g, 2 mmol) were carried out in a similar way (for reaction times see Table 1).

**2-Isopropylamino-5-nitropyridine (2a):** Yield 165 mg, 91% (method *A*); 151 mg, 83% (method *B*); 40 mg, 22% (method *C*). Yellow solid. M.p. 81–82 °C. $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 9.00 (d, *J* = 2.6 Hz, 1 H, 2-H), 8.17 (dd, *J* = 9.3, 2.6 Hz, 1 H, 4-H), 6.34 (d, *J* = 9.3 Hz, 1 H, 5-H), 5.40 (br. s, 1 H, NH), 4.07 [m, 1 H, $C\mathit{H}(CH_3)_2$], 1.29 ppm [d, *J* = 6.5 Hz, 6 H, $CH(C\mathit{H}_3)_2$]. $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 160.5, 147.1, 135.5, 132.9, 105.6, 43.8, 22.6 ppm. HRMS (ESI): calcd. for $C_8H_{12}N_3O_2$ [M + H]$^+$ 182.0930; found 182.0937. $C_8H_{11}N_3O_2$ (181.2): calcd. C 53.03, H 6.12, N 23.19; found C 53.25, H 5.97, N 23.42.

**2-Butylamino-5-nitropyridine (2b):** Yield 181 mg, 93% (method *A*); 178 mg, 91% (method *B*). Yellow solid. M.p. 101–102 °C (ref.[12c] 102 °C). $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 9.00 (d, *J* = 2.7 Hz, 1 H, 2-H), 8.18 (dd, *J* = 9.3, 2.7 Hz, 1 H, 4-H), 6.36 (d, *J* = 9.3 Hz, 1 H, 5-H), 5.52 (br. s, 1 H, NH), 3.40 (m, 2 H, $C\mathit{H}_2CH_2CH_2CH_3$), 1.65 (m, 2 H, $CH_2C\mathit{H}_2CH_2CH_3$), 1.44 (m, 2 H, $CH_2CH_2C\mathit{H}_2CH_3$), 0.97 ppm (t, *J* = 7.3 Hz, 3 H, $CH_2CH_2CH_2C\mathit{H}_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 160.3, 145.9, 134.7, 132.0, 104.5, 41.1, 30.3, 19.1, 12.7 ppm. HRMS (ESI): calcd. for $C_9H_{14}N_4O_2$ [M + H]$^+$ 196.1086; found 196.1086. $C_9H_{13}N_3O_2$ (195.2): calcd. C 55.37, H 6.71, N 21.52; found C 55.39, H 6.88, N 21.36.

**2-Amylamino-5-nitropyridine (2c):** Yield 171 mg, 82% (method *A*); 190 mg, 91% (method *B*). Yellow solid. M.p. 60–61 °C (heptane). $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 9.00 (d, *J* = 2.7 Hz, 1 H, 2-H), 8.18 (dd, *J* = 9.3, 2.7 Hz, 1 H, 4-H), 6.34 (d, *J* = 9.3 Hz, 1 H, 5-H), 5.36 (br. s, 1 H, NH), 3.38 (m, 2 H, $C\mathit{H}_2CH_2CH_2CH_2CH_3$), 1.66 (m, 2 H, $CH_2C\mathit{H}_2CH_2CH_2CH_3$), 1.39 [m, 4 H, $CH_2CH_2(C\mathit{H}_2)_2CH_3$], 0.93 ppm (t, *J* = 7.1 Hz, 3 H, $CH_2CH_2CH_2CH_2C\mathit{H}_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 161.4, 147.1, 135.7, 133.0, 105.4, 42.4, 29.1, 28.9, 22.4, 13.9 ppm. HRMS (ESI): calcd. for $C_{10}H_{16}N_3O_2$ [M + H]$^+$ 210.1243; found 210.1251. $C_{10}H_{15}N_3O_2$ (209.2): calcd. C 57.40, H 7.23, N 20.08; found C 57.13, H 7.34, N 19.88.

**2-Benzylamino-5-nitropyridine (2d):** Yield 147 mg, 64% (method *B*). Yellow solid. M.p. 131–132 °C (heptane) (ref.[12a] 130–131 °C). $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.90 (s, 1 H, 2-H), 8.15 (d, *J* = 9.2 Hz, 1 H, 4-H), 7.34 (m, 5 H, Ph), 6.37 (d, *J* = 9.2 Hz, 1 H, 5-H), 6.14 (br. s, 1 H, NH), 4.61 ppm (d, *J* = 3.7 Hz, 2 H, $C\mathit{H}_2Ph$). $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 161.1, 146.8, 137.3, 136.1, 133.1, 129.0, 128.0, 127.5, 105.8, 46.3 ppm. HRMS (ESI): calcd. for $C_{12}H_{12}N_3O_2$ [M + H]$^+$ 230.0930; found 230.0929. $C_{12}H_{11}N_3O_2$ (229.2): calcd. C 62.87, H 4.84, N 18.33; found C 63.05, H 4.67, N 18.62.

**2-Pyrrolidino-5-nitropyridine (2e):** Yield 97 mg, 50% (method *A*); 191 mg, 99% (method *B*). Yellow solid. M.p. 135–136 °C. $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 9.05 (d, *J* = 2.7 Hz, 1 H, 2-H), 8.17 (dd, *J* = 9.4, 2.7 Hz, 1 H, 4-H), 6.31 (d, *J* = 9.4 Hz, 1 H, 5-H), 3.57 (m, 4 H, α-$CH_2$ pyrrolidino), 2.08 ppm (br. s, 4 H, β-$CH_2$ pyrrolidino). $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 158.7, 146.9, 134.5, 132.4, 105.1, 47.4, 25.3 ppm. HRMS (ESI): calcd. for $C_9H_{12}N_3O_2$ [M + H]$^+$ 194.0930; found 194.0929. $C_9H_{11}N_3O_2$ (193.2): calcd. C 55.95, H 5.74, N 21.75; found C 56.21, H 5.86, N 21.53.

**5-Nitro-2-piperidinopyridine (2f):** Yield 145 mg, 70% (method *A*); 203 mg, 98% (method *B*). Yellow solid. M.p. 83–84 °C (ref.[12a] 82.5–83.5 °C). $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 9.01 (d, *J* = 2.8 Hz, 1 H, 2-H), 8.15 (dd, *J* = 9.6, 2.8 Hz, 1 H, 4-H), 6.55 (d, *J* = 9.6 Hz, 1 H, 5-H), 3.74 (t, *J* = 5.9 Hz, 4 H, α-$CH_2$ piperidino), 1.57–1.82 ppm (m, 6 H, β-$CH_2$ and γ-$CH_2$ piperidino). $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 160.2, 146.7, 134.3, 132.8, 104.4, 46.2, 25.7, 24.5 ppm. HRMS (ESI): calcd. for $C_{10}H_{14}N_3O_2$ [M + H]$^+$ 208.1086; found 208.1086. $C_{10}H_{13}N_3O_2$ (207.2): calcd. C 57.96, H 6.32, N 20.28; found C 58.19, H 6.08, N 19.98.

**2-Morpholino-5-nitropyridine (2g):** Yield 148 mg, 71% (method *A*); 201 mg, 96% (method *B*); 31 mg, 15% (method *C*). Yellow solid. M.p. 143–144 °C (ref.[12a] 141.8–142.3 °C). $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 9.03 (d, *J* = 2.7 Hz, 1 H, 2-H), 8.22 (dd, *J* = 9.4, 2.7 Hz, 1 H, 4-H), 6.57 (d, *J* = 9.4 Hz, 1 H, 5-H), 3.81 [t, *J* = 5.3 Hz, 4 H, $O(CH_2)_2$], 3.75 ppm [t, *J* = 5.3 Hz, 4 H, $N(CH_2)_2$]. $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 160.5, 146.3, 135.3, 133.1, 104.5, 66.5, 45.1 ppm. HRMS (ESI): calcd. for $C_9H_{12}N_3O_3$ [M + H]$^+$ 210.0879; found 210.0888. $C_9H_{11}N_3O_3$ (209.2): calcd. C 51.67, H 5.30, N 20.09; found C 51.39, H 5.22, N 20.38.

**2-Hexamethyleneimino-5-nitropyridine (2h):** Yield 181 mg, 82% (method *B*). Yellow solid. M.p. 66–67 °C (heptane). $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 9.05 (dd, *J* = 2.8, 0.4 Hz, 1 H, 2-H), 8.17 (dd, *J* = 9.5, 2.8 Hz, 1 H, 4-H), 6.45 (dd, *J* = 9.5, 0.4 Hz, 1 H, 5-H), 3.74 (m, 4 H, α-$CH_2$ hexamethyleneimino), 1.82 (m, 4 H, β-$CH_2$ hexamethyleneimino), 1.58 ppm (m, 4 H, γ-$CH_2$ hexamethyleneimino). $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 160.2, 146.9, 134.4, 132.7, 104.0, 48.5, 27.3, 26.8 ppm. HRMS (ESI): calcd. for $C_{11}H_{16}N_3O_2$ [M + H]$^+$ 222.1243; found 222.1236. $C_{11}H_{15}N_3O_2$ (221.2): calcd. C 59.71, H 6.83, N 18.99; found C 59.56, H 6.74, N 19.25.

**2-Diethylamino-5-nitropyridine (2i):** Yield 27 mg, 14% (method *B*); 39 mg, 20% (method *D*); 18 mg, 9% (method *E*). Yellow solid. M.p. 75–76 °C (ref.[12a] 75.2–76.2 °C). $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 9.04 (d, *J* = 2.8 Hz, 1 H, 2-H), 8.16 (dd, *J* = 9.5, 2.8 Hz, 1 H, 4-H), 6.42 (d, *J* = 9.5 Hz, 1 H, 5-H), 3.62 [q, *J* = 7.1 Hz, 4 H, $N(C\mathit{H}_2CH_3)_2$], 1.24 ppm [t, *J* = 7.1 Hz, 6 H, $N(CH_2C\mathit{H}_3)_2$]. $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 159.5, 147.0, 134.4, 132.6, 104.0, 43.5, 12.7 ppm. HRMS (ESI): calcd. for $C_9H_{14}N_3O_2$ [M + H]$^+$ 196.1086; found 196.1091. $C_9H_{13}N_3O_2$ (195.2): calcd. C 55.37, H 6.71, N 21.52; found C 55.11, H 6.75, N 21.78.

**General Procedure for the Oxidative Alkylamination of Quinazoline (3):** To a stirred solution of quinazoline (**3**) (0.130 g, 1 mmol) in the appropriate alkylamine (10 mL) at 8–10 °C, $AgPy_2MnO_4$ (0.770 g, 2 mmol) was added in small portions over a 30 min-1 h period (see Table 2). The excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was grinded with silica gel (3–4 g), brought onto a column with silica gel (3.5 × 20 cm) and purified by flash column chromatography with dichloromethane/methanol (50:1) as the eluent to yield 4-alkylaminoquinazoline (**4**). Reactions with $KMnO_4$ (0.316 g, 2 mmol) or $AgMnO_4$ (0.454 g, 2 mmol) were carried out in a similar way (for reaction times see Table 2).

**4-Isopropylaminoquinazoline (4a):** Yield 15 mg, 8% (method *A*); 161 mg, 86% (method *B*). White solid. M.p. 175–177 °C (ref.[17] 173 °C). $^1H$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.67 (s, 1 H, 2-H), 7.83 (d, *J* = 8.3 Hz, 1 H, 8-H), 7.73 (d, *J* = 8.3 Hz, 1 H, 5-H), 7.71 (ddd, *J* = 7.6, 8.3, 1.0 Hz, 1 H, 6-H), 7.43 (ddd, *J* = 7.6, 8.3, 1.0 Hz, 1 H, 7-H), 5.70 (d, *J* = 4.1 Hz, 1 H, NH), 4.58 [m, 1 H, $C\mathit{H}(CH_2)_3$], 1.36 ppm [d, *J* = 6.5 Hz, 6 H, $CH(C\mathit{H}_2)_3$]. $^{13}C$ NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 158.8, 155.4, 149.3, 132.5, 128.5, 125.9, 120.5, 114.9, 42.9, 22.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{14}N_3$ [M + H]$^+$ 188.1188; found 188.1184. $C_{11}H_{13}N_3$ (187.2): calcd. C 70.56, H 7.00, N 22.44; found C 70.41, H 7.23, N 22.14.

**4-Butylaminoquinazoline (4b):** Yield 78 mg, 39% (method *A*); 187 mg, 93% (method *B*); 163 mg, 81% (method *D*). White solid.

M.p. 116–118 °C (ref.[17] 116 °C). $^1$H NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.67 (s, 1 H, 2-H), 7.83 (d, $J$ = 8.3 Hz, 1 H, 8-H), 7.75 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.71 (t, $J$ = 7.6 Hz, 1 H, 6-H), 7.44 (t, $J$ = 7.6 Hz, 1 H, 7-H), 6.00 (br. s, 1 H, NH), 3.67 (m, 2 H, $C\mathit{H}_2CH_2CH_2CH_3$), 1.72 (m, 2 H, $CH_2C\mathit{H}_2CH_2CH_3$), 1.47 (m, 2 H, $CH_2CH_2C\mathit{H}_2CH_3$), 0.98 ppm (t, $J$ = 7.4 Hz, 3 H, $CH_2CH_2CH_2C\mathit{H}_3$). $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 158.6, 154.4, 148.2, 131.5, 127.4, 124.9, 119.6, 114.0, 40.2, 30.4, 19.2, 12.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}N_3$ [M + H]$^+$ 202.1344; found 202.1345. $C_{12}H_{15}N_3$ (201.3): calcd. C 71.61, H 7.51, N 20.88; found C 71.92, H 7.69, N 21.03.

**4-Amylaminoquinazoline (4c):** Yield 13 mg, 6% (method *A*); 207 mg, 96% (method *B*). White solid. M.p. 109–110 °C (heptane) (ref.[17] 110 °C). $^1$H NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.66 (s, 1 H, 2-H), 7.85 (d, $J$ = 8.2 Hz, 1 H, 8-H), 7.75 (d, $J$ = 8.2 Hz, 1 H, 5-H), 7.72 (ddd, $J$ = 7.0, 8.2, 1.3 Hz, 1 H, 6-H), 7.46 (ddd, $J$ = 7.0, 8.2, 1.3 Hz, 1 H, 7-H), 5.95 (br. s, 1 H, NH), 3.67 (dt, $J$ = 5.5, 7.2 Hz, 2 H, $C\mathit{H}_2CH_2CH_2CH_2CH_3$), 1.74 (m, 2 H, $CH_2C\mathit{H}_2CH_2CH_2CH_3$), 1.42 (m, 4 H, $CH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_3$), 0.93 ppm (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_2CH_2CH_2C\mathit{H}_3$). $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 159.6, 155.5, 149.3, 132.5, 128.4, 125.9, 120.7, 115.1, 41.4, 29.2, 29.0, 22.4, 14.0 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}N_3$ [M + H]$^+$ 216.1501; found 216.1502. $C_{13}H_{17}N_3$ (215.3): calcd. C 72.52, H 7.96, N 19.52; found C 72.32, H 8.14, N 19.33.

**4-Cyclohexylaminoquinazoline (4d):** Yield 12 mg, 5% (method *A*); 198 mg, 87% (method *B*). White solid. M.p. 146–148 °C (heptane) (ref.[13c] 148–149 °C). $^1$H NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.66 (s, 1 H, 2-H), 7.81 (d, $J$ = 8.2 Hz, 1 H, 8-H), 7.73 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.69 (ddd, $J$ = 7.0, 8.3, 1.2 Hz, 1 H, 6-H), 7.42 (ddd, $J$ = 7.0, 8.2, 1.1 Hz, 1 H, 7-H), 5.63 (d, $J$ = 6.9 Hz, 1 H, NH), 4.27 [m, 1 H, H(1′) $c$-$C_6H_{11}$], 2.15 (m, 2 H, $CH_2$, $c$-$C_6H_{11}$), 1.80 (m, 2 H, $CH_2$, $c$-$C_6H_{11}$), 1.50 (m, 2 H, $CH_2$, $c$-$C_6H_{11}$), 1.29 ppm (m, 4 H, $CH_2$, $c$-$C_6H_{11}$). $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 158.7, 155.6, 149.6, 132.4, 128.7, 125.8, 120.4, 115.0, 49.7, 33.1, 25.7, 25.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}N_3$ [M + H]$^+$ 228.1501; found 228.1495. $C_{14}H_{17}N_3$ (227.3): calcd. C 73.98, H 7.54, N 18.49; found C 73.77, H 7.21, N 18.52.

**4-Benzylaminoquinazoline (4e):** Yield 214 mg, 91% (method *C*); 183 mg, 78% (method *D*). White solid. M.p. 167–168 °C (ref.[13c] 169 °C). $^1$H NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.67 (s, 1 H, 2-H), 7.84 (d, $J$ = 8.3 Hz, 1 H, 8-H), 7.77 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.71 (ddd, $J$ = 7.1, 8.3, 1.3 Hz, 1 H, 6-H), 7.45–7.31 (m, 6 H, 7-H and $C_6H_5$), 6.35 (br. s, 1 H, NH), 4.87 ppm (d, $J$ = 5.4 Hz, 2 H, $C\mathit{H}_2C_6H_5$). $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 159.4, 155.3, 149.3, 138.1, 132.7, 128.8, 128.6, 128.4, 127.9, 127.3, 127.0, 126.1, 120.8, 114.9, 45.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}N_3$ [M + H]$^+$ 236.1188; found 236.1187. $C_{15}H_{13}N_3$ (235.3): calcd. C 76.57, H 5.57, N 17.86; found C 76.82, H 5.69, N 17.54.

**4-Pyrrolidinoquinazoline (4f):** Yield 62 mg, 31% (method *C*). Yellow solid. M.p. 56–57 °C (ref.[13d] 57–58 °C). $^1$H NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.59 (s, 1 H, 2-H), 8.14 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.82 (d, $J$ = 8.3 Hz, 1 H, 8-H), 7.67 (ddd, $J$ = 7.1, 8.3, 1.2 Hz, 1 H, 6-H), 7.36 (ddd, $J$ = 7.1, 8.3, 1.2 Hz, 1 H, 7-H), 3.92 (t, $J$ = 6.6 Hz, 4 H, α-$CH_2$ pyrrolidino), 2.05 ppm (m, 4 H, β-$CH_2$ pyrrolidino). $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 159.8, 154.4, 151.4, 131.9, 128.0, 125.3, 124.4, 116.5, 51.0, 25.7 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}N_3$ [M + H]$^+$ 200.1188; found 200.1184. $C_{12}H_{13}N_3$ (199.2): calcd. C 72.33, H 6.58, N 21.09; found C 72.12, H 6.90, N 21.15.

**4-Piperidinoquinazoline (4g):** Yield 145 mg, 68% (method *C*). Yellow oil. [ref.[13c] 193–194 °C (picrate)]. $^1$H NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.71 (s, 1 H, 2-H), 7.87 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.86 (d, $J$ = 8.3 Hz, 1 H, 8-H), 7.70 (dd, $J$ = 7.1, 8.3 Hz, 1 H, 6-H), 7.42 (dd, $J$ = 7.1, 8.3 Hz, 1 H, 7-H), 3.71 (m, 4 H, α-$CH_2$ piperidino), 1.75 ppm (m, 6 H, β-$CH_2$ and γ-$CH_2$ piperidino). $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 164.9, 154.1, 151.7, 132.3, 128.5, 125.2, 125.0, 116.8, 51.0, 26.0, 24.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}N_3$ [M + H]$^+$ 214.1344; found 214.1353. $C_{13}H_{15}N_3$ (213.3): calcd. C 73.21, H 7.09, N 19.70; found C 73.23, H 6.87, N 19.91.

**4-Morpholinoquinazoline (4h):** Yield 5 mg, 2% (method *A*); 207 mg, 96% (method *C*). Yellow solid. M.p. 92–93 °C (ref.[13c] 93–94 °C). $^1$H NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.76 (s, 1 H, 2-H), 7.93 (d, $J$ = 8.4 Hz, 1 H, 5-H), 7.87 (dd, $J$ = 8.3, 1.0 Hz, 1 H, 8-H), 7.75 (ddd, $J$ = 7.0, 8.4, 1.0 Hz, 1 H, 6-H), 7.47 (ddd, $J$ = 7.0, 8.3, 1.2 Hz, 1 H, 7-H), 3.90 [t, $J$ = 4.7 Hz, 4 H, $O(CH_2)_2$ morpholino], 3.79 ppm [t, $J$ = 4.7 Hz, 4 H, $N(CH_2)_2$ morpholino]. $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 164.7, 154.0, 151.7, 132.6, 128.8, 125.6, 124.7, 116.6, 66.8, 50.3 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}N_3O$ [M + H]$^+$ 216.1137; found 216.1132. $C_{12}H_{13}N_3$ (215.2): calcd. C 66.96, H 6.09, N 19.52; found C 67.23, H 5.85, N 19.34.

**4-Hexamethyleneiminoquinazoline (4i):** Yield 73 mg, 32% (method *C*). Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.60 (s, 1 H, 2-H), 7.99 (dd, $J$ = 8.3, 1.3 Hz, 1 H, 5-H), 7.87 (dd, $J$ = 8.3, 1.3 Hz, 1 H, 8-H), 7.68 (ddd, $J$ = 7.0, 8.3, 1.3 Hz, 1 H, 6-H), 7.37 (ddd, $J$ = 7.0, 8.3, 1.3 Hz, 1 H, 7-H), 3.95 (t, $J$ = 5.8 Hz, 4 H, α-$CH_2$ hexamethyleneimino), 1.98 (m, 4 H, β-$CH_2$ hexamethyleneimino), 1.68 ppm (dt, $J$ = 6.9, 2.6 Hz, 4 H, γ-$CH_2$ hexamethyleneimino). $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 162.6, 153.8, 152.1, 131.8, 128.2, 125.5, 124.2, 115.9, 51.3, 28.5, 27.5 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}N_3$ [M + H]$^+$ 228.1501; found 228.1500. $C_{14}H_{17}N_3$ (227.3): calcd. C 73.98, H 7.54, N 18.49; found C 74.05, H 7.77, N 18.31.

**4-Diethylaminoquinazoline (4j):** Yield 56 mg, 28% (method *C*). Yellow oil (ref.[13f] oil). $^1$H NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 8.54 (s, 1 H, 2-H), 7.81 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.76 (d, $J$ = 8.3 Hz, 1 H, 8-H), 7.60 (ddd, $J$ = 7.2, 8.3, 1.0 Hz, 1 H, 6-H), 7.30 (ddd, $J$ = 7.2, 8.3, 1.0 Hz, 1 H, 7-H), 3.66 [q, $J$ = 7.0 Hz, 4 H, $N(C\mathit{H}_2CH_3)_2$], 1.31 ppm [t, $J$ = 7.0 Hz, 6 H, $N(CH_2C\mathit{H}_3)_2$]. $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 162.5, 153.9, 151.7, 131.9, 128.3, 124.7, 124.5, 116.2, 45.0, 13.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}N_3$ [M + H]$^+$ 202.1344; found 202.1345. $C_{12}H_{15}N_3$ (201.3): calcd. C 71.61, H 7.51, N 20.88; found C 71.50, H 7.22, N 20.64.

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