Selective N-Nitrosation of Amines, *N*-Alkylamides and *N*-Alkylureas by N_2O_4 Supported on Cross-Linked Polyvinylpyrrolidone (PVP–N_2O_4)

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Abstract: N_2O_4 was supported on the cross-linked polyvinylpyrrolidone (PVP) to afford a solid, stable and recyclable nitrosating agent. This reagent shows excellent selectivity for N-nitrosation of dialkyl amines in the presence of diaryl-, arylalkyl-, trialkylamines and also for secondary amides in dichloromethane at room temperature under mild and heterogeneous conditions. Also *N*-nitroso-*N*-alkyl amides can be selectively prepared in the presence of primary amides and *N*-phenylamides under similar reaction conditions. Selective N-nitrosation or dealkylation and N-nitrosation of tertiary amines can also be performed by this reagent.

Key words: N-nitrosation, amine, amide, urea, polyvinylpyrrolidone

In recent years, much attention has been paid to the chemistry and biochemistry of nitric oxide (NO) and this interest continues to expand as the range of chemical and biological functions increases.[1–3] *N*-Nitrosamines, *N*-nitrosoamides and *N*-nitrosoureas can be considered as potential nitric oxide donors[4] with interesting biological activities.[5,6] Apart from wide biological applications of nitrosamines, they have been used for the introduction of alkyl, acyl, and carboxyl groups at the α-position of secondary amines via α-metalated nitrosamines.[7a–c] Also, nitrosamines can be regarded as important precursors for the preparation of α-substituted secondary amines, α-amino ketones and α-amino acid derivatives, carboxamides, sulfonamides, hydroximamides, amino oximes, hydrazines and ν-triazoles.[7] *N*-Nitrosamines have also been used for the desulfurization of thiocarbonyl compounds.[8] In addition, their uses in industry as pesticides, antioxidants, lubricant additives and also as polar solvents have been reported.[7a,9]

N-Nitrosamines and *N*-nitrosoamides are regarded as carcinogenic compounds and special care should be taken during their synthesis and handling.[5a] Nitrosamines are usually synthesized by the reaction of secondary amines with nitrosating agents[4a,9a] such as, nitrous acid (generated in situ from sodium nitrite and acids in aqueous or chloroform/HCl media),[10] alkyl nitrites,[11] nitrosyl chloride (NOCl),[12] nitosonium tetrafluoroborate,[12] [$NO^+ \cdot crown \cdot H(NO_3)_2^-$],[13] trichloronitromethane,[14] nitrogen oxides (N_2O_3[15] or N_2O_4[16]), NO in the presence of O_2,[17] Fremy's salt,[18] *N*-haloamides and sodium nitrite under phase-transfer conditions,[19] and recently by lithium amides with NO.[20]

N-Nitrosoamides has been found to be very useful precursors for the preparation of esters,[21a,b] hyroxy compounds,[21a,b] carboxamides[21c] and thioesters.[21d] *N*-Alkyl-*N*-nitrosoureas belong to the one of the most useful classes of anticancer agents.[22d] N-Nitrosation of amides by HNO_2,[22a,b] NOCl,[22a] nitrogen oxides,[22a] $NOBF_4$ and NO in the presence of O_2,[22c] and of ureas by HNO_2,[22b,d] NOCl,[22d] nitrogen oxides,[22d] $NOBF_4$[22d] has been reported.

Due to advantages of heterogeneous systems such as simple procedure and work-up, some heterogeneous reagent systems have been developed for N-nitrosation of secondary amines. Sodium nitrite in the presence of wet SiO_2 and trichloroisocyanuric acid,[23] inorganic chloride salts (e.g. $AlCl_3$,[24a] and silica chloride[24b]), or solid acids such as oxalic acid dihydrate,[25a] iodic or periodic acid,[25b] silica sulfuric acid[26a] and Nafion-H®,[26b] have been recently reported. However, none of the reported heterogeneous reagents has been used for the selective nitrosation reactions.

Selective N-nitrosation reactions have great applications especially in peptide[27] and amino acid[27c] systems. Very limited numbers of reports are available in the literature for the selective N-nitrosation reactions. The reagents N_2O_4, NO in the presence O_2, and $NOBF_4$ have been reported to show selectivity for nitrosation only between secondary amides,[22c,27a,28] and *t*-BuONO for the nitrosation of primary versus secondary amides.[28] To the best of our knowledge, there are no reports available regarding the selective nitrosation of amines and ureas.

In continuation of our studies in the field of nitrosation and nitration of organic compounds with N_2O_4 and its organic and inorganic complexes,[29] we were interested to examine the application of PVP–N_2O_4 for nitrosation of some nitrogen containing organic compounds. Recently, we have reported on the use of linear PVP–N_2O_4 as an efficient, safe, cheap and easy to handle reagent for nitrosation of thiols and oxidation of sulfur compounds under heterogeneous conditions.[29g]

Now we introduce the cross-linked PVP–N_2O_4 or its linear form for N-nitrosation of amines, amides and ureas under heterogeneous condition with excellent selectivity between these compounds. The use of cross-linked PVP–N_2O_4 is advantageous over the linear one, since the cross-linked PVP, which is released after the reaction, is not sol-

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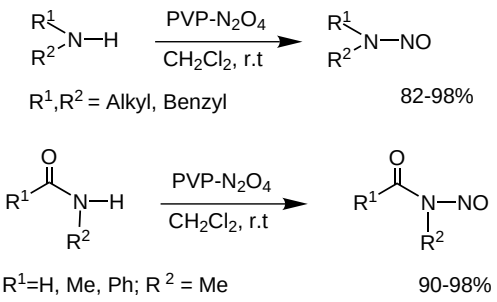
uble in most solvents and provides easier work-up procedure. This reagent was simply prepared by the reaction of cross-linked polyvinylpyrrolidone (PVP) in dichloromethane with liquid N_2O_4 at 0 °C while stirring the reaction mixture gently. Based on the amount of absorbed N_2O_4 per each unit of polymer, an 1:1 addition compound (PVP–N_2O_4) is probable. This kind of addition compound has already been proposed in the reaction of different ethers (or amines) with N_2O_4.[30a] The IR spectrum of PVP–N_2O_4 (KBr disk) showed a strong absorption band centered at 1380 cm^{-1} similar to the one, which we have observed for the linear PVP–N_2O_4 (KBr disk: 1384 cm^{-1}; CH_2Cl_2 solution: 1355 cm^{-1}) or N_2O_4 complexes of ethers or amines (CH_2Cl_2 solution: 1360 cm^{-1}). The decrease in the frequency of the carbonyl band of the cross-linked PVP–N_2O_4, (KBr disk: 1635 cm^{-1}) in comparison with the band for the free polymer, (KBr disk: 1690 cm^{-1}) could account for the interaction of N_2O_4 with the oxygen atom of the amide group in this polymeric reagent. This reagent is stable at below 0 °C and could be stored in the refrigerator for several months without loss of its weight or activity.

As shown in Scheme 1, dialkylamines and mono N-alkylamides were converted into their corresponding *N*-nitrosamines or *N*-nitrosoamides with PVP–N_2O_4 in excellent yields at room temperature (Table 1, Entries 1–21). This reagent proved to be efficient also for N-nitrosation of both monoalkyl and *N*,*N*′-dialkylureas at room temperature (Table 1, Entries 24,25), but could not nitrosate benzamide, acetanilide and urea (Table 1, Entries 22,23,26). The results of N-nitrosation of these classes of compounds are shown in Table 1.



Scheme 1

Table 1 N-Nitrosation of Dialkyl amines, *N*-Alkylamides and *N*-Alkylureas by Cross-Linked PVP–N_2O_4 in CH_2Cl_2 at Room Temperature

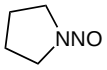
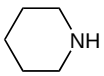
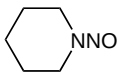
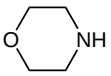
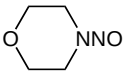
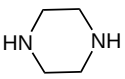
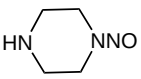
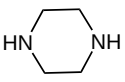
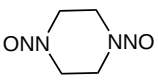
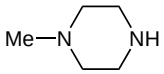
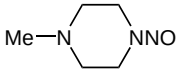
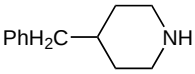
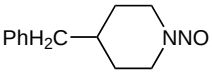
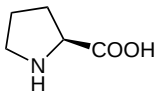
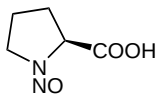
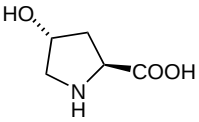
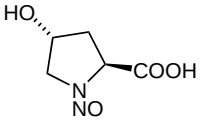
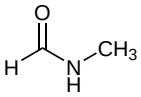
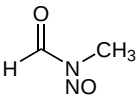
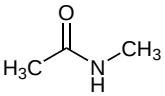
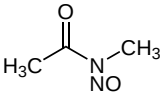
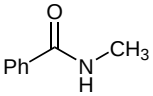
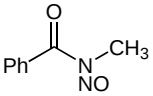
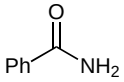
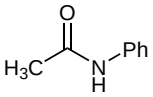
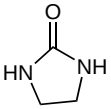
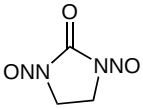
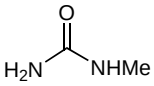
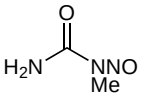
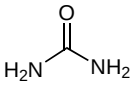
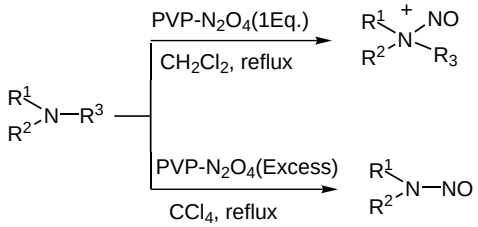
Entry	Substrate	Product	Time (Min)	Yield (%)[a]	Reference to the Product
1	Et_2NH	Et_2NNO	–[b]	95	Ref.[13–15a,26,31a,b]
2	$[HO(CH_2)_2]_2NH$	$[HO(CH_2)_2]_2NNO$	8	90	Ref.[26,32]
3	$(i\text{-}Pr)_2NH$	$(i\text{-}Pr)_2NNO$	4	85	Ref.[13–15a,20,26]
4	Bu_2NH	Bu_2NNO	2	97	Ref.[15a,18,20,31a,b]
5	$(c\text{-}C_6H_{11})_2NH$	$(c\text{-}C_6H_{11})_2NNO$	7	92	Ref.[13,19,20,23,25,26]
6	$(PhCH_2)_2NH$	$(PhCH_2)_2NNO$	5	95	Ref.[13,15a,19,26,31a]
7	$PhCH_2NHMe$	$PhCH_2N(NO)Me$	6	90	Ref.[7b–c,31a,b]
8	$PhCH_2NHEt$	$PhCH_2N(NO)Et$	5	90	Ref.[31a,b]
9	$PhCH_2NH(CH_2)_2Ph$	$PhCH_2N(NO)(CH_2)_2Ph$	5	95	Ref.[33]
10			–[b]	98	Ref.[14,23,26,31a,b,34]
11			–[b]	96	Ref.[13,14,15a,26,31,34]
12			–[b]	82	Ref.[13,14,18,23,26]
13			15	94	Ref.[23,26]
14[c]			20	98	Ref.[23,26,31c]

Table 1 N-Nitrosation of Dialkyl amines, *N*-Alkylamides and *N*-Alkylureas by Cross-Linked PVP–N_2O_4 in CH_2Cl_2 at Room Temperature (continued)

Entry	Substrate	Product	Time (Min)	Yield (%)[a]	Reference to the Product
15			9	88	Ref.[11,35]
16			4	95	Ref.[35]
17			15	98	Ref.[13,23,26]
18			20	94	Ref.[23,26]
19			150	95	Ref.[33,22b]
20			180	98	Ref.[22b]
21			210	90	Ref.[22c]
22		-[d]	180	-	-
23		-[d,e]	180	-	-
24[c]			240	90	Ref.[22b]
25			200	89	Ref.[22b,33]
26		-[d]	200	-	

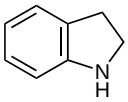
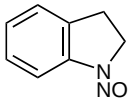
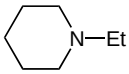
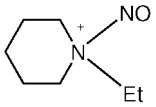
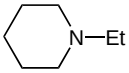
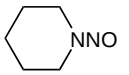
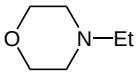
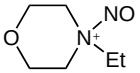
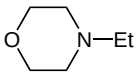
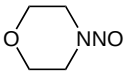
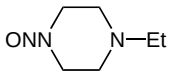
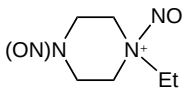
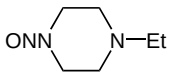
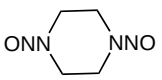
[a] Isolated yield.
[b] Spontaneous reaction.
[c] Two equivalents of the reagent were used.
[d] No reaction.
[e] Only traces (5%) of *N*-(4-nitrophenyl)acetamide was formed.



Scheme 2

Our investigation showed that the replacement of alkyl groups in amines with aryl groups strongly affects the rate of the reaction so that the nitrosations cannot occur at room temperature and needs reflux conditions. The results of N-nitrosation of different aryl amines in refluxing CCl_4 are shown in Table 2 (entries 1–6).

Table 2 N-Nitrosation of Diaryl-, Alkylarylamines, and Trialkylamines by Cross-Linked PVP–N_2O_4

Entry	Substrate	Product	Time (h)	Yield (%)[a]	Reference to the Product
1	Ph_2NH	Ph_2NNO	1	95	Ref.[13,15a,16d,26]
2	$PhNHCH_2Ph$	$PhN(NO)CH_2Ph$	6	98	Ref.[26b]
3	PhNHMe	PhN(NO)Me	1.5	92	Ref.[14,15a,26,34]
4	PhNHEt	PhN(NO)Et	2	94	Ref.[15a]
5	$PhNH(CH_2)_2OH$	$PhN(CH_2)_2OH$ NO	5.5	90	Ref.[26,32]
6			4	95	Ref.[26b,34]
7	Et_3N	Et_3N^+–NO	3[b]	95	Ref.[32]
8	Et_3N	Et_2NNO	12[c]	80	Ref.[13,14,15a,26,31a,b]
9	Bu_3N	Bu_3N^+–NO	3[b]	98	Ref.[32]
10	Bu_3N	Bu_2NNO	12[c]	75	Ref.[15a,18,20,31a]
11			2[b]	98	Ref.[31c]
12			10[c]	75	Ref.[13,14,15a,26,31]
13			2[b]	95	Ref.[31c]
14			10[c]	70	Ref.[13,14,18,26]
15			3[b]	98	Ref.[31c]
16			12[c]	70	Ref.[23,26,31c]
17	$(PhCH_2)_3N$	$(PhCH_2)_3N^+$–NO	6[b]	100	Ref.[32]
18	$(PhCH_2)_3N$	$(PhCH_2)_2N$–NO	16[c]	45	Ref.[13,15a,19,31a]

[a] Isolated yield.
[b] Reaction was performed using one equivalent of the reagent in CH_2Cl_2 under reflux condition.
[c] Four equivalents of the reagent were used in refluxing CCl_4.

Since, dealkylation and N-nitrosation of tertiary amines is an important synthetic approach for the preparation of some caged polynitramines and polynitrosamines,[30b] we studied the application of our reagent for this purpose. We observed that, PVP–N_2O_4 is a very selective reagent for nitrosation of tertiary amines. It converts tertiary amines to their corresponding *N*-nitroso derivatives or to dealkylated and N-nitrosated products, depending on the reaction conditions. N-Nitrosation reactions occurred using one equivalent of the reagent in refluxing CH_2Cl_2, while dealkylation and N-nitrosation of tertiary amines proceeded by using an excess of the reagent in refluxing CCl_4 (Scheme 2, Table 2, Entries 7–18). In comparison with the reported methods for dealkylation and N-nitrosation reactions which are usually performed with moderate yields under strongly acidic conditions (70–100% HNO_3),[31a] or excess of N_2O_4,[31b,c] similar reactions with PVP–N_2O_4 proceeds under neutral and milder reaction conditions in good yields.

Selective N-nitrosation reactions were also studied using this reagent. It was observed that when the possibility of

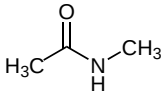
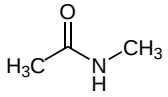
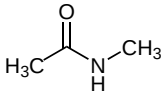
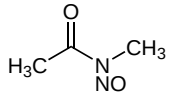
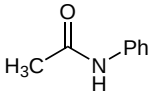
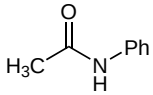
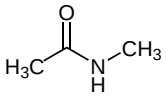
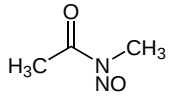
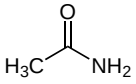
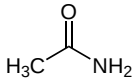
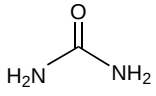
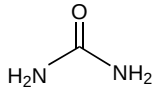
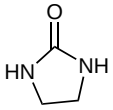
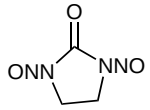
both aromatic nitrosation and N-nitrosation exist, N-nitrosation reaction preferably occurs even in the presence of activated aromatic rings. In the reaction of different aromatic amines with PVP–N_2O_4, N-nitrosation takes place quantitatively without occurrence of any aromatic nitrosation or nitration reaction (Table 2, Entries 1–6). Also, in a binary mixture of Et_2NH and anisole, no aromatic nitrosation or nitration occurred and diethylamine was converted to the corresponding *N*-nitrosodiethylamine quantitatively in CH_2Cl_2 at room temperature after 30 minutes. Selective N-nitrosation can also occur in the presence of O-nitrosation. This is demonstrated by the high yield formation of N-nitrosated products of different amino alcohols and amino acids (Table 1, Entries 2,17,18, Table 2, Entry 5).

This reagent also shows high selectivity for N-nitrosation reactions between amines, amides and ureas. Our experiments showed that excellent selectivity was observed between secondary and tertiary amines. This is shown in Table 3, Entry 1. Excellent selectivity can also be observed between dialkyl- and alkyl-, aryl- or diarylamines (Table 3, Entries 2–4). High selectivity was also observed in N-nitrosation reactions between dialkylamines and *N*-alkylamides (Table 3, Entry 5). Similarly, *N*-alkylamides can be N-nitrosated with PVP–N_2O_4 in the presence of *N*-arylamides or primary amides with excellent selectivity (Table 3, Entries 6,7). We observed that urea remained intact in the presence of dialkylurea (Table 3, Entry 8).

The advantage of using cross-linked PVP–N_2O_4 is that by a simple filtration, the solution of pure product is obtained which could be used for further synthetic purposes. In addition, The polymeric reagent was recycled (5 times) without losing its reactivity. The released polymer acts as an acid scavenger and removes the produced nitric acid from the reaction mixture to give cross-linked PVP–HNO_3. This was confirmed by comparison with a known sample of cross-linked PVP–HNO_3 (see experimental for regeneration of the reagent).

In conclusion, the use of cross-linked PVP–N_2O_4 as a stable, recycable, and easily prepared reagent provides the possibility of nitrosation of amines, amides and ureas under mild, and neutral reaction conditions. In addition, the excellent selectivity of the method and ease of work-up can be considered as strong advantages for using this reagent.

Table 3 Selective N-Nitrosation Between Different Amines, Amides, and Ureas in CH_2Cl_2 at Room Temperature

Entry	Substrates	Product[a]	Time (min)
1	Et_2NH	Et_2NNO	45
	Et_3N	Et_3N	
2	$(i\text{-Pr})_2NH$	$(i\text{-Pr})_2NNO$	30
	PhNHMe	PhNHMe	
3	$(i\text{-Pr})_2NH$	$(i\text{-Pr})_2NNO$	30
	$PhNHCH_2Ph$	$PhNHCH_2Ph$	
4	Et_2NH	Et_2NNO	30
	Ph_2NH	Ph_2NH	
5	Et_2NH	Et_2NNO	20
			
6			240
			
7			240
			
8[b]			300
			

[a] The yields determined by GC were quantitative.
[b] Two equivalents of the reagent were used.

Chemicals were purchased from Merck and Fluka chemical companies. The products were characterized by comparison of their physical data with those of known samples or by their spectral data. IR spectra were run on a Shimadzu model 8300 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250 spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV_{254} plates or by a Shimadzu Gas Chromatograph GC-14A instrument with a flame ionization detector.

Cross-Linking of Polyvinylpyrrolidone[36]

Into a 2-L beaker containing PVP K30 (50 g) was added H_2O (ca. 250 mL). The beaker was placed in a water bath and while mixing with a mechanical stirrer, $K_2S_2O_8$ (100 g) was added. The temperature of water bath was gradually raised to 80 °C. In a few minutes the contents of the beaker was converted to a gel. It was removed from the beaker and crumbled into small pieces by hand (protected with gloves) or using a blender. It was transferred to the beaker again and stirred with a mechanical stirrer at 80 °C for 4 h. The cross-linked PVP was filtered and washed several times with plenty of H_2O. It was continuously extracted with H_2O and then MeOH (each time ca.10 h). Finally, the cross-linked polymer was dried at

80 °C in a vacuum oven. The product weight was 48 g, and contained 98% of the original polymer, which was characterized by IR spectroscopy. The resulting solid was ground in a mortar to produce a yellow powder with irregularly shaped particles. The amount of CH_2Cl_2 and CCl_4 that was absorbed by the polymer after 2.5 h stirring at r.t. was found to be 0.7 and 0.6 g per gram of the cross-linked polymer, respectively.

PVP–N_2O_4[29g]

To a suspension of cross-linked PVP (10 g) in CH_2Cl_2 (200 mL) at 0 °C, was added excess of liquid N_2O_4 (7.0 mL) while stirring the solution gently. After 1 h, dry N_2 gas was bubbled through the solution in order to extrude the excess of NO_2 gas and then the solvent was evaporated. The obtained solid was dried under vacuum and was powdered in a mortar to give PVP supported N_2O_4 as a pale yellow powder (18.0 g). The capacity of the reagent was determined to be 5 mmol of N_2O_4 per gram of the polymer. The reagent could be stored in the refrigerator for several months without loss of its weight or activity.

Nitrosation of Amines; Typical Procedures

CAUTION! *N*-Nitrosamines and *N*-nitrosoamides should be regarded as potential carcinogenic compounds. The use of an efficient hood and handling with special care are highly recommended.

***N*-Nitrosopiperidine**

Cross-linked PVP–N_2O_4 (0.4 g, 2 equiv) was added to a stirred solution of piperidine (0.172 g, 2 mmol) in CH_2Cl_2 (4 mL) at r.t. Monitoring of the reaction mixture by GC showed an immediate reaction. Then the mixture was filtered. Evaporation of the solvent under reduced pressure followed by chromatography on a short column of silica gel using acetone–petroleum ether (1:9) yielded *N*-nitrosopiperidine (0.22 g, 96%); bp 217–220 °C/760 Torr (Lit.[33] bp 219 °C/760 Torr).

***N*-Nitroso-*N*-methylaniline**

A solution of *N*-methylaniline (0.107 g, 1 mmol) in CCl_4 (2 mL) was placed in a round-bottomed flask (25 mL) equipped with a condenser. Cross-linked PVP–N_2O_4 (0.2 g, 1 mmol) was added and the mixture was refluxed for 1.5 h. The mixture was then cooled and filtered. Evaporation of the solvent followed by chromatography on a short column of silica gel using acetone–petroleum ether (1:9) afforded *N*-nitroso-*N*-methylaniline (0.125 g, 92%); bp 224–226 °C/760 Torr (dec.) [Lit.[33] bp 225 °C/760 Torr (dec.)].

Dealkylation and N-Nitrosation of Triethylamine

To a solution of Et_3N (0.101 g, 1 mmol) in CCl_4 (5 mL) was added cross-linked PVP–N_2O_4 (0.8 g, 4 equimol) and the mixture was refluxed for 12 h. The mixture was then cooled and filtered. Evaporation of the solvent followed by chromatography on a short column of silica gel using acetone–petroleum ether (1:9) yielded *N*-nitrosodiethylamine (0.082 g, 80%) as a pale yellow liquid; bp 174–176 °C/760 mm, (Lit.[23] bp 173–176 °C/760 mm).

N-Nitroso-*N*-methylurea

Cross-linked PVP–N_2O_4 (0.2 g, 1 equiv) was added to a stirred solution of *N*-methylurea (0.074 g, 1 mmol) in CH_2Cl_2 (15 mL) at r.t. Monitoring of the reaction mixture by GC showed that the reaction was complete after 200 min. The mixture was filtered. Evaporation of the solvent under reduced pressure followed by passing through a short column of silica gel using acetone–petroleum ether (1:9) as eluent gave *N*-methyl-*N*-nitrosourea (0.92 g, 89%); mp 121–123 °C (dec.) [Lit.[33] mp 123–124 °C (dec.)].

Regeneration of the Reagent PVP–N_2O_4

To regenerate the reagent, the used polymer (0.5 g) was stirred in CH_2Cl_2 (10 mL) in the presence of basic alumina (1.0 g) for 15 min to remove the HNO_3. Then the solution was filtered and the obtained polymer (0.4 g) was reacted with N_2O_4 (see above) to give 0.72 g of the PVP–N_2O_4.

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