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Polyethylene glycol nitrite (PEG-ONO) as a novel diazotizing agent

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ABSTRACT

A polyethylene glycol nitrite (PEG-ONO) has been developed as a novel diazotizing agent. It is found to be cost effective, highly stable, easy to handle and efficient diazotizing agent. This reagent has been explored in various well known reactions occurring via the diazonium intermediate. Non-volatile nature of PEG-ONO reduces its exposure to the user and thereby minimizes the risk of nitrite toxicity.

INTRODUCTION

Nitrites are a class of reagents used as the source of nitrosonium ion in diazotization and nitrosation reactions. Both the reactions play important roles in synthesis of pharmaceuticals, agrochemicals and dyes. Since the discovery of diazotization by sodium nitrite in 1861¹, these reactions are used in many chemical processes including synthesis of azo dyes, aromatic halogenation^{2, 3}, palladium-catalyzed cross coupling reactions such as Matsuda-Heck, Suzuki-Miyaura, carbonylative couplings, Stille, and C-heteroatom couplings.^{4, 5} Diazotization reactions are widely used as a method of electrografting to develop modified materials including carbon nanotubes, metals and semiconductors useful in variety of applications⁶. Motivated by the intense commercial and scientific interest in diazotization reactions, various modifications have been reported; including the use of modified organic nitrites.

The conventionally used inorganic nitrites have limited applicability in many cases where the presence of water is undesirable. The formation of undesired side products; for example phenols formed in Sandmeyer reaction, occurs in aqueous medium.⁷ Alkyl nitrites such as amyl nitrite and butyl nitrite can be used in non-aqueous diazotization reactions,⁸ however these nitrites are volatile and difficult to handle⁷, as on inhalation these volatile nitrites show toxic effects on central nervous system, cardiovascular system, hematologic system and ocular organs. Interaction of inhaled nitrites with endogenous trivalent nitrogen compounds can produce nitrosamines, known to be carcinogens.⁹

One of the twelve principles of green chemistry states that chemical products should be designed to preserve efficacy of the function while reducing toxicity.¹⁰ Glycol nitrite has been reported as a diazotizing agent¹¹ which is non-volatile and easy to handle. However after releasing the nitrosonium ion, it is converted to ethylene glycol which is toxic.¹² Various other

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3 nitrite reagents based on polymers, ionic liquid and organosilane nanoparticles have been
4 reported.¹³⁻¹⁶ With an objective to overcome drawbacks of the available organic nitrites, an idea
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6 of polyethylene glycol nitrite (PEG-ONO) was conceived.
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10 Polyethylene glycol (PEG) is attractive from the green chemistry point of view since it is
11 nonvolatile, nontoxic, biodegradable, economical and readily available. It is widely used in
12 pharmaceuticals, cosmetics and food industries. PEG is well known to synthetic chemists as an
13 environmentally benign solvent and catalyst¹⁷⁻²⁶. Thus PEG was derivatized to obtain a novel
14 organic nitrite which is non-volatile, easy to handle and economic. In the present paper, we
15 explore synthesis, characterization and synthetic applicability of the developed nitrite reagent in
16 some well-known reactions.
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29 EXPERIMENTAL SECTION

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31 **Synthesis of PEG nitrite.** Sodium nitrite (4.74 g, 0.069 moles) was dispersed in 25 g of
32 polyethylene glycol 400 under stirring at room temperature. Concentrated sulfuric acid (1.7 ml,
33 0.0343 moles) was added slowly to the dispersion under continuous stirring for 15 minutes. The
34 stirring was continued for 1 hour followed by vacuum filtration to collect PEG-ONO as
35 colourless filtrate. It was stored in amber colour glass bottle at 2-8°C for further use. It was
36 characterized by elemental analysis, FTIR, NMR, mass spectrometry, UV-visible spectroscopy,
37 DSC and TGA (SI).
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48 **Synthesis of azo dyes using PEG-ONO** (Scheme 2, Table 2). 4-nitroaniline (7 mmol, 1g) was
49 dissolved in conc. HCl (2.6 ml) and water (2.5 ml) at 40°C. The solution was cooled to 0°C under
50 continuous stirring; to which PEG-ONO (3.86 g) was added slowly over 1 hour. The reaction
51 mixture was tested for the presence of nitrite by starch iodide paper test. The reaction mixture
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was added slowly to the 20 ml aqueous solution of 1-naphthol (1.04 g) and sodium hydroxide (1.4 g) under vigorous stirring at temperature below 10°C. After 15 minutes stirring; the reaction mixture was acidified with conc. HCl followed by filtration of the dye. It was washed with cold water and dried under vacuum. The synthesized dyes are known compounds and were characterized by matching their melting points with the literature values and FT-IR (SI).

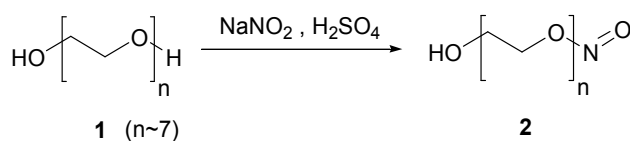
Halogenation reactions using PEG-ONO. Amberlyst 15 (6 g) was soaked in a 30 ml acetonitrile for 20 minutes; to which aromatic amine (10.74 mmol) was added under stirring. To it, PEG-ONO (4 g) was added slowly with continuous stirring. The reaction mixture was tested for the presence of nitrite by starch iodide paper test. Metal halide (16.11 mmol) was added to the reaction mixture at 25-30°C. Reaction temperature was heated slowly to 60-65°C. Heating was continued for 5 minutes after complete evolution of nitrogen. After cooling the reaction mixture to room temperature, it was filtered to recover Amberlyst-15. Cold water was added to the reaction mixture. Product was extracted with ethyl acetate. Organic layer was washed with sodium bicarbonate solution followed by drying over sodium sulfate. Ethyl acetate was evaporated under reduced pressure to get the product. Crude product was purified by column chromatography. All the synthesized compounds are known and melting points of solid products were matched with the reported melting points. Representative compounds were characterized by FT-IR and ¹H NMR (SI).

RESULTS AND DISCUSSION

Synthesis of PEG nitrite

Initially, PEG-ONO synthesis was attempted by a protocol used for synthesis of alkyl nitrites (Scheme 1).⁷ Accordingly; aqueous solution of sodium nitrite in PEG 400 (1) was treated with

conc. H_2SO_4 at $0-5^\circ\text{C}$ to get PEG-ONO (2). In contrast to the alkyl nitrites, PEG-ONO could not be separated from water due to their miscibility. Neat reaction of PEG with sodium nitrite and conc. H_2SO_4 at $0-5^\circ\text{C}$ was not feasible due to high viscosity of PEG at low temperature. Further modifications led to a facile procedure in which PEG-ONO could be prepared at ambient temperature by adding conc. H_2SO_4 to the sodium nitrite dispersion in PEG. In contrast to alkyl nitrites, no brown fumes were observed during preparation or handling of PEG-ONO.



Scheme 1. Synthesis of polyethylene glycol nitrite (PEG-ONO)

Characterization of PEG nitrite

Purity of PEG-ONO was confirmed by single peak in HPLC chromatogram (Figure 1) and elemental analysis (Anal. Calcd. C 48.11, H 8.33, N 3.51, O 40.06; Found: C 47.087, H 8.866, N 3.502 and O 40.545, $\text{C}_{16}\text{H}_{33}\text{N}_1\text{O}_9 \cdot \text{H}_2\text{O}$) (SI). It was characterized by FT-IR and ^1H NMR spectroscopy (SI). Characteristic IR peak around 1643 cm^{-1} (asymmetrical stretching of nitrite esters group) confirmed the formation of PEG-ONO. Stability study using UV-visible spectrophotometer showed that PEG-ONO is stable for one week at $2-8^\circ\text{C}$. 22% of PEG-ONO was found to be degraded over 3 months storage at $2-8^\circ\text{C}$. (SI)

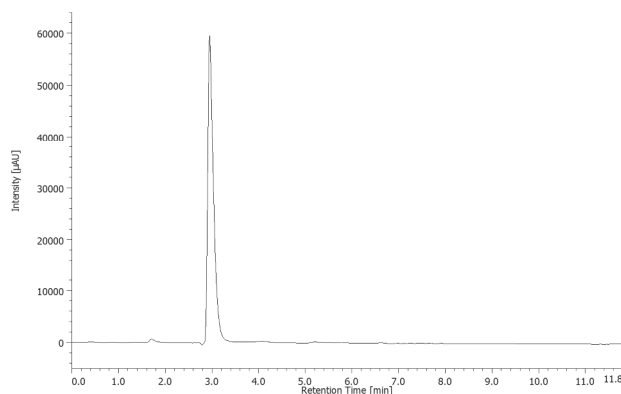


Figure 1. Chromatogram of PEG-ONO (C-18 column, Methanol-Acetonitrile (60:40) mobile phase, flow rate 1 ml/min at 25°C)

The diazotization potential of PEG-ONO was revealed by kinetic study of diazotization of 4-nitroaniline in aqueous acidic media by UV spectroscopy. The absorbance at 380 nm, which corresponds to 4-nitroaniline (Figure 2), decays during 20 min and tends to a plateau. This indicates that 4-nitroaniline is transformed into the corresponding diazonium demonstrating the reactivity of PEG-ONO as diazotizing agent.

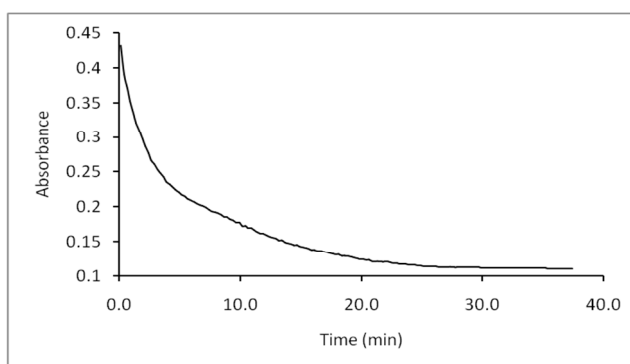


Figure 2. Plot of absorbance of 4-nitroaniline (0.28mM) in HCl (0.56mM) and PEG-ONO (0.42 mM) as a function of time at 380 nm

Risk of using hazardous chemical is function of hazard and exposure (Eq. 1)¹⁰.

$$\text{Risk} = f(\text{hazard})(\text{exposure}) \quad (\text{Eq. 1})$$

Risk of using alkyl nitrites is due to their volatile nature which increases its exposure and known toxicity during use. We rationalized that PEG-ONO is safer to use as compared to alkyl nitrite due to its stable and non-volatile nature. Calorimetric analysis (Figure 3) indicated that PEG-ONO is stable up to 82°C. DSC shows endotherms at 82°C and 214°C. The first endotherm at 82°C may be due to loss of nitrite group. TGA indicated that there was negligible weight loss up to 82°C and 8% weight loss was observed up to 150°C (Figure 4). Nonvolatile nature of PEG nitrite reduces its potential exposure and therefore the risk of using it. As there is no exotherm in DSC, we can conclude that PEG-ONO would not be explosive.

PEG-ONO is advantageous over other nitrites in many aspects as presented in Table 1.

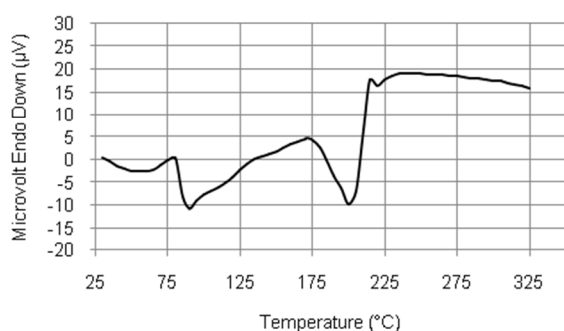


Figure 3. Differential Scanning Calorimetric analysis (DSC) of PEG-ONO (heating in nitrogen atmosphere at the rate of 10°C/min)

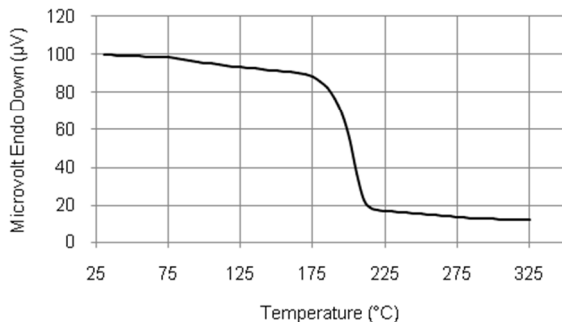


Figure 4. Thermogravimetric analysis (TGA) of PEG-ONO (heating in nitrogen atmosphere at the rate of 10°C/min)

Table 1. Comparison of PEG-ONO with the reported organic nitrites^a

Nitrite	Stability	Volatility	Cost	Fate after reaction
R-ONO	Unstable	Volatile	Economic	Alcohol
NOBF ₄ ²⁷	Unstable	Nonvolatile	Economic	HF, BF ₃
Resin-ONO ¹³	Stable	Nonvolatile	Expensive	Resin
Glycol nitrite ¹¹	Stable	Nonvolatile	Economic	Ethylene glycol
IL-ONO ¹⁴	Stable	Nonvolatile	Expensive	IL
PEG-ONO	Stable	Nonvolatile	Economic	PEG

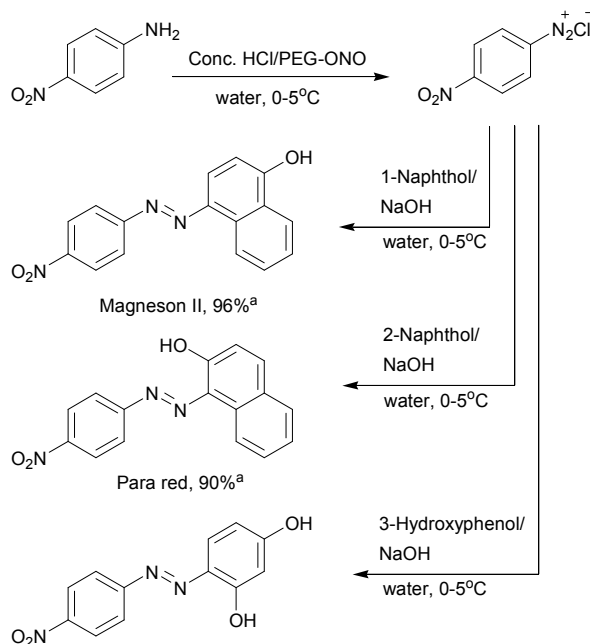
^aR-ONO- alkyl nitrite, IL-ionic liquid

Application of PEG-ONO in diazotization reactions

Synthesis of azo compounds is a topic of interest due to wide applications in various fields such as textiles, biomedicines, optics, reprography, electronic devices and sensors.²⁸⁻³¹

Syntheses of azo dyes from 4-nitroaniline were achieved using PEG-ONO (Scheme 2). This reaction in water at room temperature (~25°C) yielded traces of dye (Table 2, entries 1-2). The

same observation was noted when PEG 400 was used as a solvent instead of water (Table 2, entries 3-4). When diazotization was conducted at lower temperature in water; quantitative yield of azo dye was obtained (Table 2, entry 5). PEG-ONO was successfully used in synthesis of different azo compounds in good yields (Scheme 2). The synthesized compounds are known and were characterized by melting points and FT-IR ($\nu_{\text{N=N}} = 1500\text{--}1550\text{ cm}^{-1}$) (SI).



Scheme 2. Diazotization-coupling reactions, ^aIsolated yields, Magneson II M.P.: $279\text{--}282^\circ\text{C}$ (Lit. $281\text{--}282^\circ\text{C}$)³², Para red M.P.: $246\text{--}250^\circ\text{C}$ (Lit. $249\text{--}250^\circ\text{C}$)³³, Azoviolet M.P.: $183\text{--}186^\circ\text{C}$ (Lit. $183\text{--}185^\circ\text{C}$)³³

Table 2. Optimization studies of diazotization of 4-nitroaniline by PEG-ONO followed by coupling with 1-naphthol^a

Entry	Solvent	Acid	Temperature (°C)	Yield ^b
1	Water	HCl	25°C	Traces
2	Water	-	25°C	-
3	PEG 400	HCl	25°C	Traces
4	PEG 400	-	25°C	-
5	Water	HCl	0-5°C	96
6	Water	p-TSA	25°C	98
7	Water	Amberlyst 15	25°C	96
8	THF	Amberlyst 15	25°C	90
9	ACN	Amberlyst 15	25°C	92

^a 4-nitroaniline (7 mmol, 1g) in conc. HCl (2.6 ml) and solvent (15 ml) was reacted with PEG-ONO (3.86 g) over 1 hour followed by coupling with 1-naphthol (1.04 g) in presence of sodium hydroxide (1.4 g). ^b Isolated yield

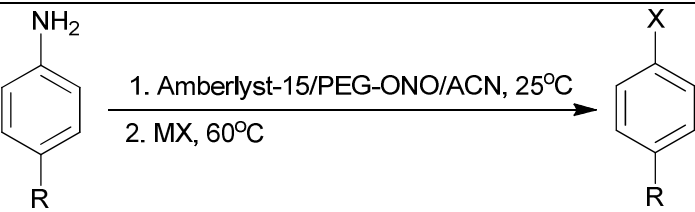
Though diazotization of aromatic amines has been extensively studied, stability of arenediazonium salts has remained the point of concern to chemists. Intrinsic instability of arenediazonium salts containing anions such as chloride or sulfate makes them difficult to isolate and store. Literature on arenediazonium stabilization by complexation with electron donors prompted us to study stability of arenediazonium ions in presence of PEG since it has ether linkages³⁴. Findings in optimization studies of diazotization by PEG-ONO (Table 3, entry 1, 2, 3, 5) led us to reject our hypothesis of diazonium ion or salt being stabilized by PEG. The counter ion of diazonium cation plays an important role in its stability. It is well known that tosylate anion stabilizes the diazonium cation. Diazotization can be achieved at room temperature by

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3 using p-toluene sulfonic acid (Table 2, entry 6) but p-toluene sulfonic acid goes to the effluents
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5 after dediazonation reactions. We used polystyrene supported sulfonic acid (Amberlyst 15)³⁵
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7 which could be recycled and achieved good yields of the azo dye. PEG-ONO also showed
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9 diazotization reactions in non-aqueous solvents including acetonitrile and tetrahydrofuran. (Table
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12 2, entries 8-9).

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15 With the optimized conditions of diazotization in hand, PEG-ONO was explored in Sandmeyer
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17 reaction which is the most widely used method for synthesis of aryl halides by copper catalysis.^{2,}
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19 8, 36, 37 Conventional Sandmeyer reaction is one pot process for synthesis of iodo, bromo and
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21 chloro-arenes from aromatic amines via diazotization-dediazonation. Phenols are generated as
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23 byproducts in these reactions when water is used as a solvent. This drawback is overcome by
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25 using alkyl nitrites in non-aqueous conditions⁸. We modified the Sandmeyer protocol by using
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27 PEG-ONO as a diazotizing agent which excludes the hazards of alkyl nitrites.
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32 Diazonium salts formed in situ were subjected to dediazonation-halogenation by heating in the
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34 presence of suitable halide source. The desirable conditions for dediazonation step are different
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36 for iodination, bromination and chlorination. Iodination reaction does not need copper catalyst
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38 due to favourable oxidation potential of iodide anion.³⁸ Various iodoarenes were obtained in
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40 good yields using potassium iodide as a source of iodide anion (Table 3, entries 1-5).
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42 Bromination and chlorination reactions were executed using cupric bromide and cupric chloride
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44 respectively. Good yields of bromo and chloroarenes were obtained using PEG-ONO as
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46 diazotizing agent (Table 3, entries 6-15).
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Table 3. Halogenation reactions using PEG-ONO^a

						
Run	R	MX	Time (min)		M.P. (Lit.) (°C)	% Yield ^b (reported yield)
			Step 1	Step 2		
1	-H	KI	30	20	Liq.	85 (75) ³⁹
2	-CH ₃	KI	25	30	32-34 (33-35)	88 (83) ³⁹
3	-OCH ₃	KI	25	25	45-48 (48-52)	70 (61) ³⁵
4	-COCH ₃	KI	50	10	80-82 (82-84)	72 (75) ³⁵
5	-NO ₂	KI	40	10	173-176 (172-177)	85 (81) ³⁵
6	-H	CuBr ₂	30	25	Liq.	70 (65) ⁴⁰
7	-CH ₃	CuBr ₂	25	30	26-29 (26-29)	85 (60) ⁴⁰
8	-OCH ₃	CuBr ₂	25	30	Liq.	58 (77) ⁸
9	-COCH ₃	CuBr ₂	50	25	45-50 (49-53)	87 (91) ⁴¹
10	-NO ₂	CuBr ₂	40	25	124-126 (124-127)	88 (87) ⁴²
11	-H	CuCl ₂	30	30	Liq.	76
12	-CH ₃	CuCl ₂	25	30	Liq.	71
13	-OCH ₃	CuCl ₂	25	30	Liq.	60 (45) ⁴²
14	-COCH ₃	CuCl ₂	50	30	Liq.	75 (83) ⁴¹
15	-NO ₂	CuCl ₂	40	30	83-85 (82-86)	75 (87) ⁴²

^a aromatic amine (10.74 mmol) was reacted with PEG-ONO (4 g) in the presence of Amberlyst 15 (6 g) in a 30 ml acetonitrile; followed by addition of metal halide (16.11 mmol) and heating until complete evolution of nitrogen. ^b Isolated yield

Conclusions

We have developed polyethylene glycol nitrite (PEG-ONO) as a diazotizing agent. PEG-ONO is privileged by intrinsic properties of PEG due to which it becomes safer to use. We present this development as a case of reducing risk of toxic reagent by decreasing its exposure to user due to its non-volatile nature. Diazotization using PEG-ONO was optimized and followed by coupling reactions with various phenols to yield commercially important azo dyes. Iodo-, bromo- and chloroarenes can be synthesized in good yields starting from aromatic amines by one-pot Sandmeyer protocol utilizing PEG-ONO as diazotizing agent. Properties of PEG including non-volatility, stability, easy availability and low cost make the PEG-ONO green diazotizing agent.

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge.

Supporting Information (PDF). Experimental details, Kinetic study and Spectral data.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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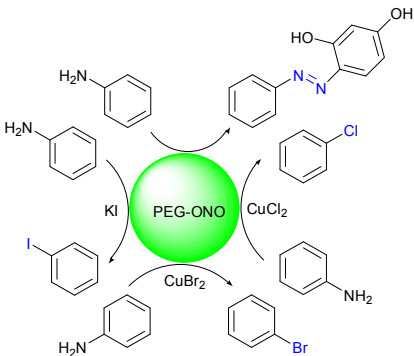
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Polyethylene glycol nitrite (PEG-ONO) as a novel diazotizing agent

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Synopsis: A polyethylene glycol nitrite (PEG-ONO) is a novel diazotizing agent having wide applicability. Non-volatility, stability, easy availability and low cost make it a green reagent.