

Article

***N*-Halosuccinimides as Precatalysts for *C*-, *N*-, *O*-, and *X*-Nucleophilic Substitution Reactions of Alcohols under Mild Reaction Conditions**

Njomza Ajvazi ^{1,*}  and Stojan Stavber ^{1,2} ¹ Jožef Stefan International Postgraduate School, Jamova 39, 1000 Ljubljana, Slovenia; stojan.stavber@ijs.si² Jožef Stefan Institute, Jamova 39, 1000 Ljubljana, Slovenia

* Correspondence: njomza.ajvazi@rezonanca-rks.com; Tel.: +383 44 258 553

Received: 6 April 2020; Accepted: 20 April 2020; Published: 24 April 2020



Abstract: *N*-halosuccinimides (chloro, bromo, and iodo, respectively) were introduced, tested, and applied as efficient and non-metal precatalysts for *C*-, *N*-, *O*-, and *X*-nucleophilic substitution reactions of alcohols under solvent-free reaction conditions (SFRC) or under high substrate concentration reaction conditions (HCRC) efficiently and selectively, into the corresponding products.

Keywords: alcohols; *N*-halosuccinimides; C–C or C–heteroatom bond formation; solvent-free; green chemistry

1. Introduction

The development of protocols for the transformation of organic compounds following the principles of green chemistry [1] is currently one of the main trends in organic synthesis. In accordance with the principle of atom economy, effective catalytic approaches, replacement of volatile or toxic organic compounds used as solvents with safer reaction media is one of the main challenges in organic synthesis.

Since alcohols are readily available and inexpensive alkylating agents, their nucleophilic substitution is an important and attractive process used in the synthesis of organic compounds, which offers a potential impact on the environment, resulting in water as the only side product of the reaction.

In order to apply the direct transformation of a hydroxyl group often an additional activation is inescapable [2].

Many related transformations, including the use of Brønsted and Lewis acids, metal ions, or other supporters in a substoichiometric amount, have been reported by several reviews [3–13] and recent related advanced reports [14–18]. However, the requirement of toxic or expensive reagents, environmentally undesirable solvents, a high concentration of the mediator, prolonged reaction time, or high temperature make such a method less attractive from the green chemical aspect. Accordingly, it was essential to design environmentally friendly synthetic protocols for the C–C and C–heteroatom bond formation. A group of organic compounds bearing an active *N*-halogen bond, *N*-halosuccinimides (NXSs) (chloro, bromo, and iodo), are an inexpensive, commercially available, easy-to-handle, and metal-free compounds, employed for oxidation, hydroxyhalogenation or halogenation reactions [19,20]. NXSs have attracted significant interest as mediators for comprehensive organic transformations [21–28]. However, the use of NXSs as the mediator for the direct transformation of alcohols forming C–C or C–heteroatom bonds has not been discovered so far.

In our continuous research on developing greener synthetic routes [29–31], we wish to report herein the introduction of NXSs as a non-metal substoichiometric mediator for the comprehensive transformations of alcohols bearing newly C–C or C–heteroatom bonds, under SFRC or under HCRC.

2. Results and Discussion

Initially, diphenylmethanol **1** has been chosen as the model substrate to investigate the efficiency of *N*-halosuccinimides as a mediator of the process and to find the best reaction conditions for alcohol transformation (Table 1). As can be seen from Table 1 the transformation of diphenylmethanol **1** in the presence of methyl alcohol **2** in the absence of any of the NXSSs, no reaction has occurred (entry 1, Table 1). The transformation of diphenylmethanol **1** mediated by *N*-halosuccinimides in the presence of MeOH **2** under HCRC gave ether **3** (entries 2–4), while in the absence of MeOH under SFRC, dimerization has been observed, affording the dimeric ether **4**, (entry 5, Table 1). Under the typical reaction conditions in the dark or the presence of radical scavenger, the quantitative conversion of starting material **1** into the corresponding product **3** was established (entries 6–7, Table 1).

Table 1. Optimal reaction conditions for the highest conversion of diphenylmethanol **1** into the (methoxymethylene)dibenzene **3** in the presence of NXSSs as mediators under HCRC ^a.

Entry	NXS	Mol %	Reaction Conditions	Conversion ^b (%) of 1	Relative Distribution ^b (%)	
					3	4
1	-	-	MeOH (1mmol), 70–75 °C, 6 h	-	-	-
2	NIS	3	MeOH (1mmol), 70–75 °C, 6 h	100	100	-
3	NCS	3	MeOH (1mmol), 70–75 °C, 6 h	100	92	5 ^c
4	NBS	3	MeOH (1mmol), 70–75 °C, 6 h	100	92	5 ^c
5	NIS	2	70–75 °C, 3.5 h	100	-	100
6	NIS	2	In the dark, MeOH (1 mmol), 70–75 °C, 6 h	100	100	-
7	NIS	2	TEMPO (10 mol %), MeOH (1 mmol), 70–75 °C, 6 h	100	100	-

^a Reaction conditions: diphenylmethanol **1** (0.5 mmol). ^b Determined from ¹H NMR spectra of isolated crude reaction mixtures. ^c Benzophenone 3%.

Furthermore, we investigated the role of *N*-halosuccinimides as the mediators for the direct C–C bond formation by direct coupling reactions of secondary benzyl alcohol with various types of electron-rich compounds, including 1,3-dicarbonyl compounds or electron-rich alkene under SFRC. We have examined the reaction of diphenylmethanol **1** with dibenzoylmethane **7** under SFRC, and results are summarized in Table 2. The transformation of diphenylmethanol **1** in the presence of dibenzoylmethane **7** under SFRC in the absence of any of the NXSSs, no reaction has occurred (entry 1, Table 2). In the presence of *N*-chlorosuccinimide (NCS) as the mediator, we did not observe any conversion of the diphenylmethanol **1** (entry 2), while in the presence of *N*-bromosuccinimide (NBS) a low conversion of the diphenylmethanol **1** into the dimeric ether **4** was observed (entry 3). Moreover, in the presence of *N*-iodosuccinimide (NIS) as the mediator, the coupling of benzyl moiety with **7** took place, providing efficiently and selectively the corresponding product **8** with the new C–C bond formed between the benzyl carbon atom and C-2 carbon of dicarbonyl target **7** (entries 4 and 5). Under the typical reaction conditions in the dark or the presence of radical scavenger, the efficient and selective transformation of diphenylmethanol **1** into the corresponding product **8** was observed (entries 6–7, Table 2).

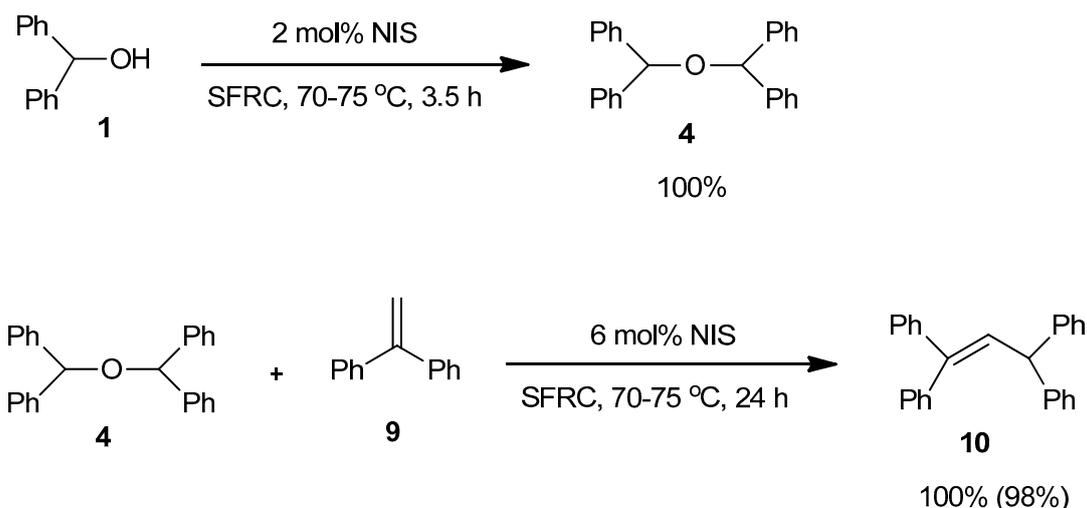
In order to support the assumption that the dimeric ether **4** might be the intermediate of this dehydrative coupling [32], few control reactions were performed (Scheme 1). Under the typical conditions when diphenylmethanol **1** was efficiently and selectively converted into dimeric ether **4**, it was applied as a starting material in the reaction with 1,1-diphenylethene **9** providing the

corresponding substituted alkene **10** in quantitative yield. With **9** providing the corresponding substituted alkene **10** in quantitative yield.

Table 2. The effect of substoichiometric amounts of NXS on conversion of diphenylmethanol **1** with dibenzoylmethane **7** under SFRC ^a.

Entry	NXS	Mol %	Conversion ^b (%) of 1	Relative Distribution ^b (%)	
				8	4
1	-	-	0	-	-
2	NCS	3	-	-	-
3	NBS	3	4	-	4
4	NIS	3	100	100	-
5	NIS	1	100	100	-
6 ^c	NIS	1	100	100	-
7 ^d	NIS	1	100	100	-

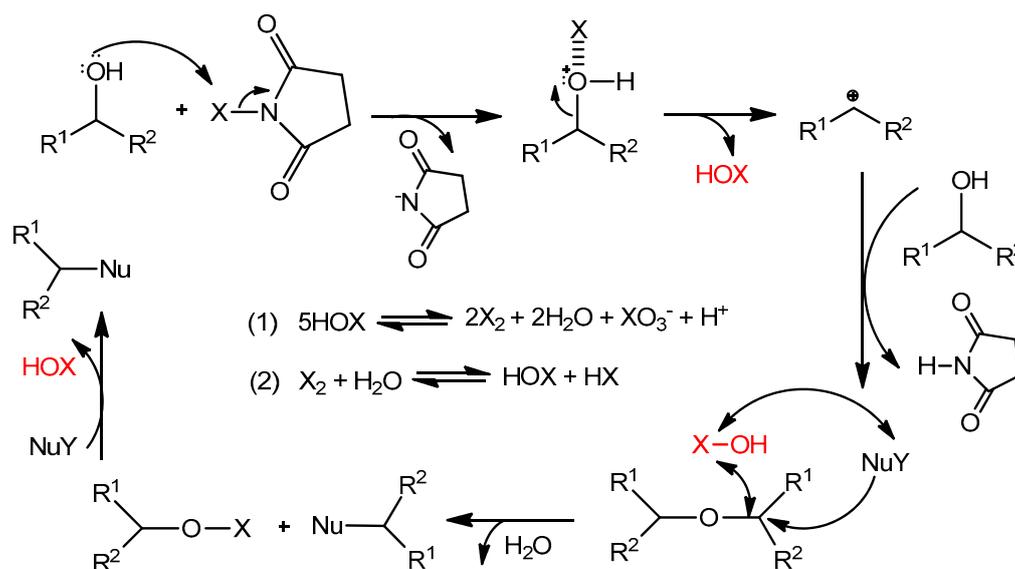
^a Reaction conditions: diphenylmethanol **1** (0.5 mmol), dibenzoylmethane **7** (0.5 mmol), 70–75 °C, 24 h. ^b Determined from ¹H NMR spectra of isolated crude reaction mixtures. ^c In the dark. ^d TEMPO (10 mol %).



Scheme 1. Control reactions.

Based on the results of the control experiment presented in (Scheme 1), the proposed reaction pathway is presented in (Scheme 2). It was reported that the R-X bond of halosuccinimides as the precatalysts was activated by its reaction with the addition of Lewis base. Therefore, it seems plausible that transient halogen bonding could be responsible for the catalytic effect of NXS [33,34].

The term halogen bonding which is defined as non-covalent interaction of a halogen atom X in one molecule with a negative site in another, such as the lone pair electrons of a Lewis base [35,36]. The halogen bonding adducts are not the activated species. Rather, halonium (X^+) transfer will generate the intermediate forming succinimide anion and HOX, which further promotes the course of the reaction. HOX decomposes by disproportionation to X_2 and HXO^3 . It is well known that X_2 forms HOX and HX in reactions with water, where HOX regenerate for following catalysis. Thus, the water resulting as an only side product of the reaction might be acting as a supporter in acceleration of the reaction.

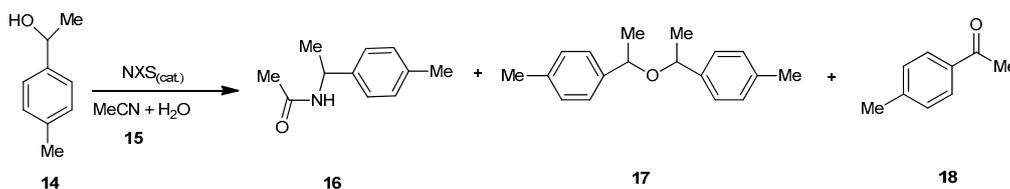


Scheme 2. Plausible reaction course.

The assumption that NXs are actually precatalysts producing HOX, X_2 , and protons during the process while these species could catalyze nucleophilic substitutions seems to be reasonable [37]. The discrimination between the oxidation process observed in the case of the use of molar excess of NXs (1.3 to 2 equivalent excess) [26–28] was achieved using substoichiometric amounts of NIS and by the selection of alcohols, which could after realizing hydroxyl group form, through resonance or strong inductive effect, stabilize carbocation intermediates which readily collapse with present nucleophile sources. Alkyl alcohols or some primary benzyl alcohols were inactive under our reaction conditions. In contrast, in some cases of secondary alcohols, the formations of trace amounts of oxidation products were observed besides target products (see Tables).

Furthermore, we studied the role of *N*-halosuccinimides as mediators for direct C–N bond formation in the reaction of the alcohol with acetonitrile and water solution, and results are summarized in Table 3. The transformation of 1-(*p*-tolyl)ethan-1-ol **14**, with acetonitrile **15** in the absence of any of the NXs, no reaction occurred (entry 1, Table 3), while, in the presence of *N*-halosuccinimides as the mediator the corresponding *N*-acyl benzyl product **16** (entries 2–4), in moderate to high yield was observed, accompanied with the formation of a small amount of dimeric ether **17** (entry 4) and oxidized alcohol **18** (entries 2–4, Table 3). We found that NCS and NIS were slightly more convenient mediators for this transformation than NBS. Under the typical reaction conditions in the dark or the presence of radical scavenger, the high conversion of starting material **14** into the corresponding product **16** was established, accompanied by the formation of a small amount of dimeric ether **17** and oxidized alcohol **18** [38] (entries 5–6, Table 3).

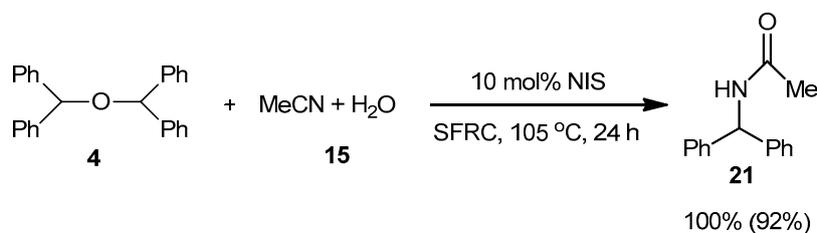
In order to support the assumption that the dimeric ether **4** might be the intermediate of this dehydrative coupling [32], few control reactions were performed (Scheme 3). Under the typical conditions when diphenylmethanol **1** was efficiently and selectively converted into dimeric ether **4** In order to support the assumption that the dimeric ether **4** might be the intermediate of the reaction course, few control reactions were performed (Scheme 3). Under the typical conditions when diphenylmethanol **1** was efficiently and selectively converted into dimeric ether **4** (Scheme 1), which was used as a starting material instead of **1** in the reaction with MeCN/H₂O **15** providing the corresponding *N*-acyl benzyl product **21** in nearly quantitative yield (Scheme 3).

Table 3. The effect of NXS as the mediator on conversion of 1-(*p*-tolyl)ethan-1-ol **14** in acetonitrile solution ^a.

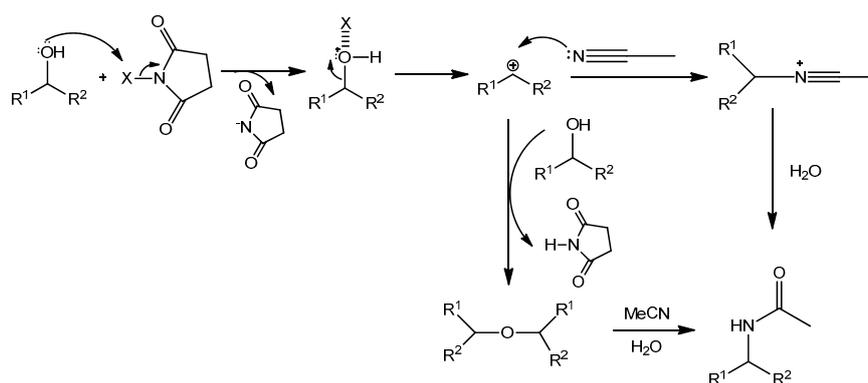
Entry	NXS	Mol %	Conversion ^b (%) of 14	Relative Distribution ^b (%)		
				16	17	18
1	-	-	-	-	-	-
2	NBS	10	78	67	-	11
3	NCS	10	82	72	-	10
4	NIS	10	84	80	2	2
5 ^c	NIS	10	84	80	2	2
6 ^d	NIS	10	84	80	2	2

^a Reaction conditions: 1-(*p*-tolyl)ethan-1-ol **14** (0.5 mmol), MeCN (1/2 mL), H₂O (2 mmol), 70–75 °C, 24 h.

^b Determined from ¹H NMR spectra of isolated crude reaction mixtures. ^c In the dark. ^d TEMPO (10 mol %).

**Scheme 3.** Control experiment.

According to these results, the dimeric ether **4** can generate the benzylic carbocation which can be trapped by MeCN to generate a nitrilium ion followed by the presence of water providing the corresponding product **21**. However, another probable pathway could be a direct reaction between carbocation and MeCN [39,40] (Scheme 4).

**Scheme 4.** Plausible reaction pathway.

The catalytic effect of NIS was applied for tertiary alkyl alcohol, in the reaction of etherification of α,α -dimethylbenzenepropanol **5** with MeOH under HCRC (entry 1, Table 4). The efficient and selective transformation was observed in the reaction with tertiary benzyl alcohol. The 2-phenylpropan-2-ol **33** was readily catalyzed by NIS providing the corresponding product **34** in nearly quantitative yield (entry 2, Table 4).

The stereochemical course of the etherification was monitored by the reaction between (S)-(-)-1-phenylethanol **11** and MeOH **2** in the presence of NIS providing the corresponding product **12** in moderate yield (entry 3, Table 4) accompanied with a small amount of acetophenone **13**. The specific rotation of pure product **12** gave the value $[\alpha] = +15^\circ$, revealing that we are not dealing with completely S_N1 or S_N2 processes but with the combination of both. It seems that the dimerization is the S_N1 , and final etherification is the S_N2 process. The details of this analysis are given in Supplementary Materials. In the case of the reaction of primary benzyl alcohol **27**, only a trace amount of benzaldehyde was observed (entry 4, Table 1).

Furthermore, under the typical reaction conditions, we checked the reaction of primary and tertiary alcohol with dibenzoylmethane **7** in the presence of NIS as the mediator under SFRC. In contrast, no reaction was observed with benzyl alcohol **27** as the type of primary alcohol due to lower reactivity and triphenylmethanol **36** as the type of tertiary alcohol, which may be attributed to the steric hindrance (entries 6 and 7, Table 4).

Additionally, the catalytic effect of NIS for direct C–C bond formation by direct coupling of phenyl substituted alkene with secondary benzyl alcohol under SFRC was studied. NIS as the mediator was found to most efficiently and selectively promote the direct coupling of diphenylmethanol **1** with 1,1-diphenylethene **9** under SFRC, furnishing the corresponding substituted alkene **10** in nearly quantitative yield (entry 8, Table 4).

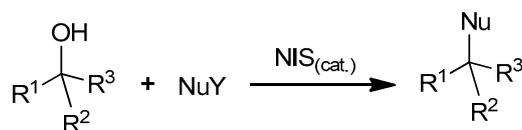
On the other hand, we checked the reactions of primary and tertiary alcohol with aqueous acetonitrile **15** in the presence of NIS as the mediator under SFRC, no reaction was observed with benzyl alcohol **27** (only a trace amount of benzaldehyde was observed) and triphenylmethanol **36**, which may be attributed to the steric hindrance (entries 9 and 10, Table 4).

Additionally, the direct coupling of aniline [41], bearing deactivated group **19**, with diphenylmethanol **1** in the presence of NIS as the mediator under SFRC, afforded the corresponding *N*-alkylated compound in high yield **20** accompanied with a small amount of oxidized alcohol (entry 10, Table 4). By increasing the temperature to 105 °C, the direct coupling of diphenylmethanol **1**, 1-phenylethanol **11** with acetonitrile and water solution **15** in the presence of NIS as the mediator afforded the corresponding *N*-acyl benzyl products **21** and **22** (entries 12 and 13, Table 4) in nearly quantitative yield.

Table 4. Nucleophilic substitution of alcohols using NIS mediator ^a.

Entry	Bond Formation	R ¹ , R ² , R ³	NuY	Product	Conversion. ^b (%) (Yield ^c (%))
1	C–O	R ¹ = R ² = Me R ³ = (CH ₂) ₂ Ph 5	MeOH 2		74 (64)
2		R ¹ = Ph, R ² = R ³ = Me 33	MeOH 2		93 (90)
3		R ¹ = Ph, R ² = H, R ³ = Me 11	MeOH 2		67 ^f (61) ^g

Table 4. Cont.



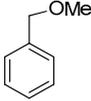
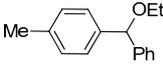
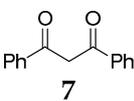
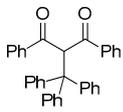
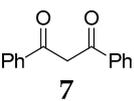
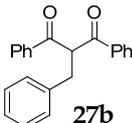
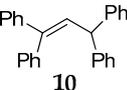
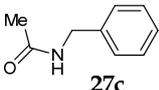
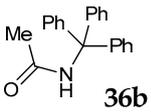
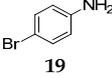
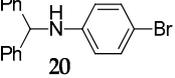
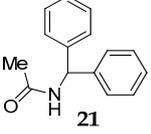
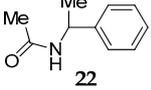
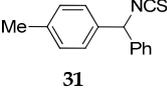
Entry	Bond Formation	R ¹ , R ² , R ³	NuY	Product	Conversion. ^b (%) (Yield ^c (%))
4		R ¹ = Ph, R ² = R ³ = H 27	MeOH 2	 27a	2 ^f -
5		R ¹ = 4-MePh, R ² = H, R ³ = Ph 30	TMSOEt 23c	 32	100 ^f (89)
6	C-C	R ¹ = R ² = R ³ = Ph 36	 7	 36a	-
7		R ¹ = Ph, R ² = R ³ = H 27	 7	 27b	-
8		R ¹ = R ² = Ph, R ³ = H 1	 9	 10	100 ^e (92)
9	C-N	R ¹ = Ph, R ² = R ³ = H 27	MeCN/H ₂ O 15	 27c	8 ^f -
10		R ¹ = R ² = R ³ = Ph 36	MeCN/H ₂ O 15	 36b	-
11		R ¹ = R ² = Ph, R ³ = H 1	 19	 20	85 ^f (79)
12		R ¹ = R ² = Ph, R ³ = H 1	MeCN/H ₂ O 15	 21	100 ^f (90)
13		R ¹ =Ph, R ² =H, R ³ =Me 11	MeCN/H ₂ O 15	 22	100 ^f (93)
14		R ¹ = 4-MePh, R ² = H, R ³ = Ph 30	TMSNCS 23b	 31	100 (97)

Table 4. Cont.

$$\text{R}^1\text{C}(\text{OH})(\text{R}^2)\text{R}^3 + \text{NuY} \xrightarrow{\text{NIS}_{(\text{cat.})}} \text{R}^1\text{C}(\text{Nu})(\text{R}^2)\text{R}^3$$

Entry	Bond Formation	R ¹ , R ² , R ³	NuY	Product	Conversion. ^b (%) (Yield ^c %)
15 ^h	C-Cl	R ¹ = 3-NO ₂ Ph, R ² = R ³ = H 24	TMSCl 23a		[42]
16		R ¹ = 3-NO ₂ Ph, R ² = R ³ = H 24	TMSCl 23a		91 ^d (76)
17 ^h		R ¹ = Ph, R ² = R ³ = H 27	TMSCl 23a		69 (65) [42]
18		R ¹ = Ph, R ² = R ³ = H 27	TMSCl 23a		100 ^d (88)
19 ^h		R ¹ = 4-MePh, R ² = H, R ³ = Me 14	TMSCl 23a		90 (86) [42]
20		R ¹ = 4-MePh, R ² = H, R ³ = Me 14	TMSCl 23a		100 (98)
21 ^h		R ¹ =Ph, R ² =R ³ =Me, 33	TMSCl 23a		100 (98) [42]

^a Reaction conditions: alcohol (0.5–1 mmol), NuY (0.5 mmol–2 mL), NIS (1–10 mol %), 50–105 °C, 6.5–48 h.

^b Determined from ¹H NMR spectra of the isolated crude reaction mixture. ^c Purified products. ^d Dimeric ether 6%–8%. ^e Oxidized alcohol and dimeric ether 4%. ^f Oxidized alcohol 2%–10%. ^g Specific rotation [α] = +15°. ^h Without catalyst.

We further investigated the impact of *N*-halosuccinimide as a mediator in reactions of primary benzyl alcohol with trimethylchlorosilane (TMSCl) **23a** under SFRC. Primary benzyl alcohol bearing a strong deactivated group was not converted into the corresponding product using TMSCl [42]. Thus, we studied the impact of *N*-halosuccinimides as a mediator on the course of reaction of 3-nitrobenzyl alcohol **24** with TMSCl under SFRC. Gratifyingly, the addition of a substoichiometric amount of NIS was found to effectively and selectively promote the reaction of 3-nitrobenzyl alcohol **24** with TMSCl under SFRC (entries 15 and 16, Table 4). To increase the yield of 1-(chloromethyl)-3-nitrobenzene **25**, different concentrations of the mediator were employed, and the results are given in the Supplementary Materials (Table S1). The role of NIS as the mediator was further examined in the improvement in yields of the chlorinated products. In the case of benzyl alcohol **27**, 1-(*p*-tolyl)ethanol **14** using TMSCl under mediator-free and SFRC the good- to high-yielding formation of the corresponding chlorides **28**

and **29** were accompanied by 10% of the symmetric ethers in both cases [42]. In the case of the reaction of benzyl alcohol **27** by adding NIS as the mediator, quantitative conversion of the starting material into the corresponding chloride **29** was observed, while only a small amount of dimer was detected as the side product (entries 17 and 18, Table 4). In the case of 1-(*p*-tolyl)ethanol **14**, the improvement of 98% yield **28** without the formation of the dimeric ether was attained by adding the NIS as the mediator (entries 19 and 20, Table 4).

The efficient and selective transformation was observed in the case with 2-phenylpropan-2-ol **33** into the corresponding product **35** [42] (entry 21, Table 4).

Inspired by this results with TMSCl **23a**, we performed the reactions of phenyl(*p*-tolyl)methanol **30** as the model compound under the mentioned reaction conditions, using (trimethylsilyl)isothiocyanate (TMSNCS) **23b** or ethoxytrimethylsilane (TMSOEt) **23c** as the sources of nucleophiles where isothiocyanate and ethoxy were introduced successfully into organic molecules **31** and **32** (entry 14 and 5, Table 4).

The collected results in Table 4 are organized primarily stressing the type of bond formation mediated by NIS as the most efficient and selective catalyst among the NXSs, enhancing the green chemical profiles of these transformations.

In order to check the thermal stability of *N*-halosuccinimides under reaction conditions, the thermal gravimetric analysis (TGA) on the NCS, NBS, and NIS catalysts were performed. It was detected that the degradation had occurred at none of the catalysts at the temperature range 25–200 °C.

3. Materials and Methods

All chemicals used for synthetic procedures were purchased from commercial sources ((Merck, Darmstadt, Germany; Sigma Aldrich, St. Louis, MO, USA) Reactions were monitored by thin-layer chromatography (TLC) (with silica gel/TLC cards, DC-Alufolien-Kieselgel, Sigma-Aldrich, St. Louis, MO, USA). For the detection of compounds on chromatographic plates, a UV (Camag, Muttenz, Switzerland) lamp (254 nm) was used. Column chromatography (CC) was performed with silica gel Kieselgel 60 (particle size: 0.063–0.200 mm, Fluka, Sigma Aldrich). Nuclear magnetic resonance (Varian INOVA 300 NMR instrument, ¹H: at 303.0 MHz, ¹³C: at 76.2 MHz) using CDCl₃ as the solvent with SiMe₄ (TMS) as an internal reference and melting points (open capillary tube methodology; uncorrected, by Buchi 535 equipment) were used for identification and structure elucidation. General procedure for etherification of alcohols mediated by *N*-halosuccinimide on half mmol scale:

A mixture of benzyl alcohol (0.5–1 mmol) and *N*-halosuccinimide as a precatalyst (3–10 mol %), which had been powdered in a mortar in the case of solid-state reactants, was transferred to a 4 mL screw-capped vial, finally added eventual liquid component alkyl alcohol (1 mmol–1 mL) and heated at 70–75 °C for 6–24 h.

The reaction was observed by TLC. After reaction completion, the reaction mixture was cooled to room temperature; dissolved in EtOAc (3 × 5 mL); washed with saturated Na₂S₂O₃ (2 × 3 mL), saturated NaHCO₃ (2 × 3 mL), and water (2 × 5 mL); and the collected organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed by evaporation under reduced pressure providing the corresponding product.

General procedure for new carbon-carbon bond formation through β-dicarbonyl compound in organic molecule mediated by NIS on half mmol scale:

A mixture of benzyl alcohol (0.5 mmol), β-dicarbonyl compound (0.5 mmol), and NIS (1 mol %) which had been powdered in a mortar, was transferred to a 4 mL screw-capped vial and heated at 70–75 °C for 24 h. The reaction was observed by TLC. After reaction completion, the reaction mixture was cooled to room temperature; dissolved in EtOAc (3 × 5 mL); washed with saturated Na₂S₂O₃ (2 × 3 mL), saturated NaHCO₃ (2 × 3 mL) and water (2 × 5 mL); and the collected organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed by evaporation under reduced pressure providing the corresponding product.

General procedure for new carbon-carbon bond formation through electron rich C=C bond in organic molecules mediated by NIS on half mmol scale:

A mixture of benzyl alcohol or dimeric ether (0.5 mmol), alkene (0.5 mmol), and NIS (6 mol %), which had been powdered in a mortar in the case of solid-state reactants was transferred to a 4 mL screw-capped vial, finally, eventual liquid component was added, and it was heated at 70–75 °C for 24 h.

The reaction was observed by TLC. After reaction completion, the reaction mixture was cooled to room temperature, dissolved in EtOAc (3 × 5 mL), washed with saturated Na₂S₂O₃ (2 × 3 mL), saturated NaHCO₃ (2 × 3 mL) and water (2 × 5 mL). Through the anhydrous Na₂SO₄ the collected organic layers were dried, and the solvent was voided by evaporation under reduced pressure.

General procedure for new carbon-nitrogen bond formation in organic molecules mediated by NIS on half mmol scale:

In a 4 mL screw-capped vial, a mixture of benzyl alcohol (0.5 mmol), acetonitrile (0.5 mL), water (2 mmol) and NIS (10 mol %), or a mixture of solid reaction components previously powdered in a mortar was transferred: benzyl alcohol (0.5 mmol), aniline (0.55 mmol) and NIS (10 mol %). The vial was then heated at 70–105 °C for 24–48 h. The reaction was observed by TLC. When the reaction was completed, the reaction mixture was cooled to room temperature, dissolved in EtOAc (3 × 5 mL), washed with saturated Na₂S₂O₃ (2 × 3 mL), saturated NaHCO₃ (2 × 3 mL) and water (2 × 5 mL), and the collected organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed by evaporation under reduced pressure providing the corresponding product.

General procedure for halo functionalization of organic compounds using trimethylsilyl derivatives mediated by NIS on half mmol scale:

A mixture of benzyl alcohol (0.5 mmol) and NIS (2–10 mol %) which had been powdered in a mortar in the case of solid-state reactants, was transferred to a 4 mL screw-capped vial, then trimethylsilyl derivatives (0.55 mmol) added and stirred at rt (room temperature) or heated at 70–75 °C for 6.5–25 h. The progress of the reaction mixture was monitored by TLC. When the reaction was completed, the reaction mixture was cooled to room temperature, dissolved in ethyl acetate (15 mL), washed with saturated Na₂S₂O₃ (6 mL), saturated NaHCO₃ (6 mL) and water (10 mL), and the collected organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed by evaporation under reduced pressure providing the corresponding product.

4. Conclusions

In conclusion, *N*-halosuccinimides (chloro, bromo, and iodo, respectively), were introduced, tested, and applied as efficient and metal-free substoichiometric mediators for reactions of a comprehensive range of alcohols with various type of electron-rich organic molecules or reactive anionic species thus forming new carbon-carbon or carbon-heteroatom bonds in target alcohol molecules. Leading reactions enhanced green chemical profiles of these valuable transformations under solvent-free reaction conditions or high concentration reaction conditions.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/10/4/460/s1>, detailed experimental data, ¹H-NMR and ¹³C-NMR spectra of isolated final products and experimental data related to thermal analysis.

Author Contributions: Conceptualization, S.S.; formal analysis, N.A. and S.S.; investigation, N.A. and S.S.; methodology, N.A. and S.S.; writing—original draft, N.A. and S.S.; writing—review and editing, N.A. and S.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Slovene Human Resources Development and Scholarship Fund (contract: 11011-9/2011), Slovenian Research Agency (contract: Programme P1-0134).

Acknowledgments: The authors are grateful to the Slovenian NMR Centre at the National Institute of Chemistry, Ljubljana, Slovenia, Prof. U. Grošelj for the specific rotation measurements, Prof. P. Bukovec for the TGA analysis of *N*-halosuccinimides, and K. Čebular for sharing her knowledge.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; and in the decision to publish the results.

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