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An Alternative to Nitromethane as Solvent: The Promoting Influence of Nitro-Functionalized Imidazolium Salts for Synthesis and Catalysis

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Abstract: Nitromethane, a volatile and toxic organic compound, is commonly used as solvent for organic and catalytic reactions. In order to find an alternative for this specific nitro-containing organic solvent, the performance of some nitro-functionalized imidazolium salts such as 1-methyl-3-(4-nitrobenzyl)imidazolium hexafluorophosphate, 1-methyl-3-(4-nitrobenzyl)imidazolium tetrafluoroborate, 1-methyl-3-(4-nitrobenzyl)imidazolium bis(trifluoromethanesulfonyl)-amide and 1,2-dimethyl-3-(4- nitrobenzyl)imidazolium hexafluorophosphate, was examined in some reactions including trimethylsilylation of alcohols with hexamethyldisilazane, ring-opening reactions of 2-aryl-3,4-dihydropyrans with thiophenols or thiols, and a copper- mediated oxidative coupling of alkynes. As expected, these imidazolium salts can indeed replace nitromethane in these reactions. Particularly, the imidazolium salt along with the metal catalyst, if involved, can be easily recovered and reused without significant loss of activity. The use of these nitro-functionalized imidazolium salts as alternative solvents for nitromethane not only confers a green aspect to the reaction system, but also facilitates a rational design of a catalytic system with the concept of green chemistry.

Keywords: nitro-functionalized imidazolium salts; oxidative coupling of alkynes; ring-opening of dihydropyran with nucleophiles; trimethylsilylation of alcohols with hexamethyldisilazane

Introduction

One of the biggest problems posed to the chemical industry is to continuously deal with the fact that all chemical plants rely heavily on toxic, hazardous and flammable organic solvents.[1] Organic solvents used in most of the synthetic processes in the chemical industry evaporate into the atmosphere with detrimental effects on the environment as well as human health. Most of the time, these volatile organic solvents are expensive to purchase, difficult to recycle or reuse, and impractical to dispose of without incurring substantial costs and/or adversely affecting the environment and/or personnel.

In order to solve these problems, the replacement of organic solvents, which are volatile and toxic, with environmentally benign one, has gained much attention.[2] In order to make the replacement acceptable for the industry, it has to be done in a way that does not stifle the technological development and that can be accomplished with moderate economical cost. Furthermore, new solvents should lead to the same, or even more benefits than the traditional ones. Therefore, replacing a traditional solvent in an industrial process with a new one is not a simple task, and many aspects as well as their relative importance must be considered and balanced.[3]

Nitromethane is the simplest organic nitro compound that has been widely used as a solvent in organic reactions, separations, and purifications. Today, data concerning the hazardous properties of nitromethane are easily available in many handbooks. Be-

cause nitromethane can detonate and cause serious harm to people, in order to handle this solvent uneventfully, some unsafe conditions should be avoided during its uses.[4] In some cases, for example, when it is mixed with a few percent of certain compounds such as amines, acids, and bases, nitromethane is "sensitized" and can be easily detonated. However, because of its specific effect exhibited in some organic reactions,[5] the risk does not seem noticeable for many researchers who are using this solvent in combination with strong acidic catalysts.[6]

In order to minimize the risk of using nitromethane as solvent, it is necessary to develop alternative solvents to such a nitro-containing compound. The particular properties of nitromethane are most likely relying on the nitro group present in its molecular structure. To find an alternative solvent for nitromethane, we have to keep the nitro part in the new solvent molecule, and strategically avoid all the negative effects, such as volatility, toxic and risk problems. For this purpose, we turned to one of the advantages of ionic liquid materials with tunable physical properties. By changing the anion and cation, ionic liquids can be prepared varying in polarity, viscosity, density, melting point, and miscibility/solubility properties. These considerations are driving our efforts in developing an alternative molten salt solvent for nitromethane, and now we wish to report the use of the title compounds in organic synthesis and catalysis.

A common method to prepare a functionalized ionic liquid involves generally the use of a haloalkane that contains a functional group as a quaternization reagent for the *N*-alkylimidazole. However, to find a reagent that contains both a nitro group and an aliphatic haloalkane fragment is not very easy. Fortunately, Liu and his co-workers have described the synthesis of some nitro-functionalized imidazolium ionic liquids quite recently.[7] In Liu's report, 4-nitro-(bromomethyl)benzene was used as a key quaternization reagent to react with 1-alkylimidazole to form some 1-alkyl-3-(4-nitrobenzyl)-1*H*-imidazolium bromide salts, which can then be used in the ion-exchange synthesis as precursors of the nitro-functionalized imidazolium salts. Inspired by this method, we were able to synthesize four nitro-functionalized imidazolium salts, including 1-methyl-3-(4-nitrobenzyl)imidazolium hexafluorophosphate (NFIS 1), 1-methyl-3-(4-nitrobenzyl)imidazolium tetrafluoroborate (NFIS 2), 1-methyl-3-(4-nitrobenzyl)imidazolium bis(trifluoromethanesulfonyl)amide (NFIS 3), and 1,2-dimethyl-3-(4-nitrobenzyl)imidazolium hexafluorophosphate (NFIS 4) (Figure 1). It should be noted that three of these imidazolium salts, NFIS 1, NFIS 2, and NFIS 4, are solid at room temperature, and their melting points are higher than 80 °C (see Supporting Information). Therefore, these salts are not room temperature ionic liquids. In view of the fact that the nitro group

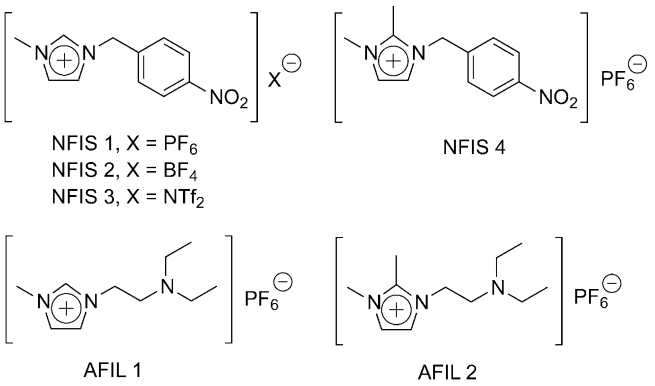


Figure 1. Functionalized 1,3-dialkylimidazolium salts.

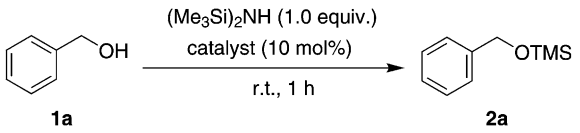
was directly attached to a phenyl ring, it is not unreasonable to expect that the potential of these imidazolium salts to explosion should be much lower than that of nitromethane. By a simple estimation on the basis of their molecular structures, data of the imidazolium salts concerning explosion should be close to that of nitrobenzene. In addition to these nitro-functionalized salts, two tertiary amine-functionalized imidazolium ionic liquids, AFIL 1 and AFIL 2, were also used in a metal-catalyzed reaction (Figure 1). Having these imidazolium salts in hand, we then focused our attention on replacing nitromethane in organic and catalytic reactions by using these nitro-functionalized imidazolium salts as environmentally benign solvents.

Results and Discussion

Silylation of hydroxy-containing compounds with hexamethyldisilazane (HMDS) is one of the most popular methods for protecting alcohols and phenols.[8] Although various catalysts have been reported to be effective for this reaction, for practical synthesis, researchers still prefer to use an old and toxic system, pyridine + chlorotrimethylsilane, in which pyridine is the solvent and chlorotrimethylsilane acts as catalyst. In order to develop an environmentally benign method for silylation with HMDS, Kim has recently reported a catalyst-free method, in which nitromethane was found to be a key promoting medium for the silylation reaction.[9] Although Kim's method avoids the use of a catalyst and is effective for a wide range of alcohols and phenols, owing to the fact that the reaction was conducted in nitromethane that is a volatile and explosive reagent, silylation with HMDS still needs improvement from the viewpoint of green synthesis.

Table 1 shows the results of silylation of benzyl alcohol with HMDS in the presence of the nitro-functionalized imidazolium salts. The reaction was conducted at room temperature and under solvent-free conditions. Because all the nitro-functionalized imida-

Table 1. Silylation of benzyl alcohol with HMDS in the presence of nitro-containing compounds.[a]



1a 2a

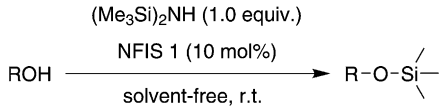
Entry	Catalyst (10 mol%)	Yield [%]
1	NFIS 1	99
2[b]	NFIS 1	73
3	NFIS 2	92
4	NFIS 3	96
5	NFIS 4	89
6	[BMIm]BF_4	21
7	[BMIm]PF_6	32
8	nitromethane	94
9	nitrobenzene	90
10[c]	NFIS 1	99
11[c,d]	NFIS 1	98
12	–[e]	0

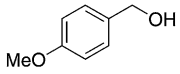
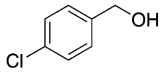
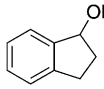
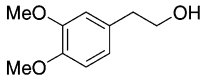
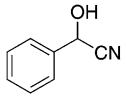
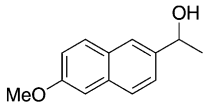
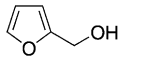
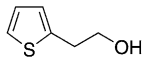
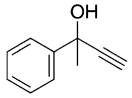
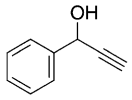
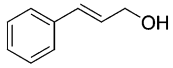
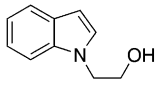
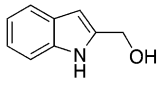
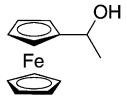
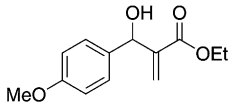
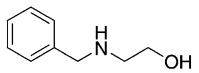
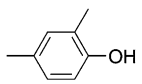
[a] Benzyl alcohol: 0.5 mmol, HMDS: 0.5 mmol, nitro-containing compound: 0.05 mmol, room temperature, 1 h.
[b] Reaction time, 0.5 h.
[c] Benzyl alcohol, 20.0 mmol.
[d] The fifth run.
[e] No catalyst was used.

zolium salts are solid at room temperature, and insoluble in the reaction mixture, the salt behaves like a solid catalyst in the model reaction. We thought that the incomplete dissolution of the ionic liquid might result in an insufficient reaction. To our surprise, as shown in Table 1, a yield of 99% was obtained after 1 h reaction time (entry 1). With a decrease of the reaction time, the yield also decreases (entry 2). It should be noted that, in our system, the imidazolium salt NFIS 1 was used in catalytic amounts (10 mol%). Under identical conditions, some other nitro-functionalized imidazolium salts, such as NFIS 2, NFIS 3, and NFIS 4, also worked well, but the yields of **2a** were slightly inferior (entries 3 to 5). Common ionic liquids, such as [BMIm]BF_4 and [BMIM]PF_6, were also used in this reaction; however, the yields obtained are rather poor (entries 6 and 7). These results imply that the nitro group might play a key role in promoting the trimethylsilylation reaction. In order to confirm our hypothesis, reactions in the presence of nitromethane and nitrobenzene were also examined under identical conditions. As we expected, high yields were obtained in these cases (entries 8 and 9), indicating that the nitro group is indeed capable of promoting the model reaction. Kim and others have shown that the silylation might start from a coordination of the oxygen atom in the nitro group to the silicon atom of HMDS, which activates the silylating reagent and allows an easy formation of the nitro-alcohol intermediate that can then eliminate ammonia to form the *O*-silyl ether.[9] Although the performances of nitromethane and nitrobenzene in the model silylation reaction are comparable with those of our nitro-functionalized salts, these systems are suffering from the difficulty of recovering the nitro-containing compounds. In this context, using the nitro-functionalized imidazolium salts as alternative substance is of prime significance because the imidazolium salt, which is a solid under the reaction conditions, could be easily recovered and reused. When the reaction scale was increased to 20 mmol, NFIS 1 could be recycled for at least 4 runs without significant loss of its activity (Table 1, entries 10 and 11). This result not only demonstrates the good recycling ability of NFIS 1, but also shows that our method is applicable for a practical synthesis. It should be noted that a blank reaction without any catalyst gave no product even after 5 h under identical conditions (entry 12). Thus, NFIS 1 was proved to be the best catalyst for the model silylation reaction.

With the optimized conditions in hand, we probed the scope of the reaction with respect to the alcoholic compounds. As evidenced by the results in Table 2, alcohols with different substituents, such as benzyl, furfuryl, 2-naphthylmethyl, 2-thienylethyl, homoveratryl, and α-cyanobenzyl, smoothly reacted with HMDS, producing the corresponding trimethylsilyl ethers generally in good yields (entries 1 to 8). In the presence of NFIS 1, cinnamyl alcohol and propargyl alcohols could be selectively converted to the silyl ethers without affecting the double and triple bonds (entries 9 to 11). Alcohols containing the indolyl group, such as 1-(2-hydroxyethyl)indole and 2-(hydroxymethyl)indole, which are generally unstable under acidic conditions, were also examined in our system, and the corresponding products were obtained in excellent yields (entries 12 and 13). 1-Ferrocenylethanol also readily participated in the reaction (entry 14). Notably, none of these reactions involved the use of an added catalyst. A Baylis–Hillman alcohol, **1p**, which was prepared from 4-methoxybenzaldehyde and ethyl acrylate and has been proven to be an active Micheal acceptor in the aza-Michael reaction,[10] can also be silylated without formation of the aza-Michael adduct with ammonia (entry 15). However, a limitation was observed with 2-(benzylamino)ethanol, which failed to participate in the silylation reaction (entry 16), likely due to a preferred interaction of the amine with the nitro group that deactivates the imidazolium salt catalyst. It is noteworthy that hydroxylgroups of phenol derivatives, such as 2,4-dimethylphenol, could also be protected with this method (entry 17), thus extending the generality of our method further. It should be noted that the yields obtained here are competitive with Kim's system,[9] but even NFIS 1 was used in only catalytic amounts. Furthermore, the easy recovery of NFIS 1 as well as the robust activity en-

Table 2. Silylation of alcohols with HMDS in the presence of NFIS 1.[a]



Entry	Alcohol		Time [h]	Product	Yield [%]
1		**1b**	1	**2b**	90
2		**1c**	1	**2c**	88
3		**1d**	1	**2d**	99
4		**1e**	1	**2e**	90
5		**1f**	1	**2f**	80
6		**1g**	1	**2g**	97
7		**1h**	1	**2h**	79
8		**1i**	1	**2i**	83
9		**1j**	1	**2j**	89
10		**1k**	1	**2k**	74
11		**1l**	1	**2l**	84
12		**1m**	1	**2m**	81
13		**1n**	1	**2n**	83
14		**1o**	1	**2o**	99
15		**1p**	1	**2p**	97
16		**1q**	1	–	0
17		**1r**	3	**2q**	84

[a] Alcohols, 1.0 mmol; HMDS: 1.0 mmol; NFIS 1, 0.1 mmol; room temperature.

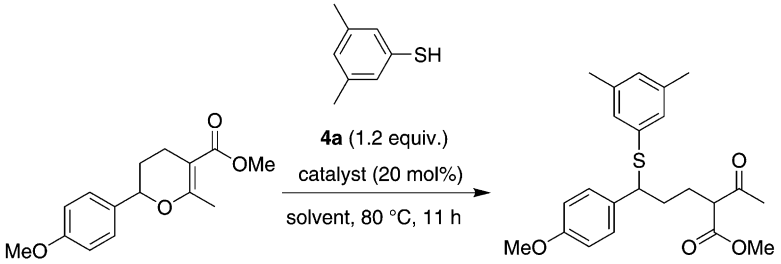
dowed our system with some attractive green parameters.

Nitro-functionalized salts were demonstrated, by means of the above-mentioned results, to be a promising alternative to nitromethane as solvent. In order to extend the applicability of this concept, we then tried to use the nitro-functionalized imidazolium salts in some catalytic systems that also involve the use of nitromethane as solvent. A literature survey showed that nitromethane has been widely used in acid-catalyzed reactions as solvent. Particularly, in the nucleophilic substitution of benzylic alcohols, nitromethane exhibited an outstanding promoting effect on the catalytic reactions.[6] Whilst the positive effect of nitromethane as solvent in acid-catalyzed organic reactions has been recognized and an explosive growth in research on acid catalysis in this solvent has been witnessed in the past few years, the potential negative effects of this nitro-containing solvent on the environment and safety aspects have been ignored almost completely. With the nitro-functionalized imidazolium salts, we might have a chance to solve these problems.

In order to evaluate the value of these nitro-functionalized imidazolium salts in assisting acid catalysis, we have to find an appropriate model reaction that not only allows a direct use of the imidazolium salt as an alternative solvent for nitromethane, but is also capable of gaining, more or less, benefit from the rational design of a new catalyst system. We have recently reported some ring-opening reactions of 2-aryl-3,4-dihydropyran and 2-alkoxy-3,4-dihydropyran with nucleophiles, such as indole and thiophenol or thiol.[11] This type of reaction was performed in nitromethane by using manganese(II) chloride or bromide as catalyst. Particularly, for the reaction of 2-aryl-3,4-dihydropyran, a mechanistic investigation revealed that an acid-catalyzed formation of a benzylcarbenium is the key to render the reaction possible.[11a] Thus, this ring-opening reaction is an acid-catalyzed reaction. Although the catalysis was found to be quite unique and effective for the synthesis of the target compounds, owing to the following drawbacks: (i) the use of nitromethane, which is toxic and explosive reagent, as a solvent; and (ii) difficulty of recycling the manganese halide catalyst; the catalytic system still needs improvement from the viewpoint of green chemistry.

We thus investigated the ring-opening reaction of 2-aryl-3,4-dihydropyran **3a** with 3,5-dimethylthiophenol, **4a**. As shown in Table 3, in nitromethane, the reaction proceeded selectively by using manganese(II) chloride tetrahydrate as catalyst, however, the yield of the desired product **5a** reached only 63% after 11 h of reaction at 80 °C (entry 1). The reactions in other solvents, such as toluene, 1,4-dioxane, DCE, and the ionic liquid [BMIm]PF_6, proceeded also sluggishly (entries 2 to 5). Surprisingly, when a combination of NFIS 1 and [BMIm]PF_6 was used as solvent, a yield

Table 3. Ring-opening reaction of **3a** with **4a** catalyzed by acids.[a]



3a **5a**

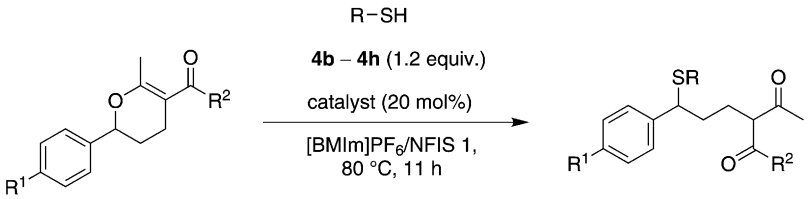
Entry	Catalyst	Solvent[b]	Co-solvent	Yield [%]
1	$MnCl_2{\cdot}4H_2O$	CH_3NO_2	–	63
2	$MnCl_2{\cdot}4H_2O$	toluene	–	trace
3	$MnCl_2{\cdot}4H_2O$	1,4-dioxane	–	trace
4	$MnCl_2{\cdot}4H_2O$	DCE	–	32
5	$MnCl_2{\cdot}4H_2O$	–	$[BMIm]PF_6$	43
6	$MnCl_2{\cdot}4H_2O$	NFIS 1	$[BMIm]PF_6$	95
7	$MnCl_2{\cdot}4H_2O$	NFIS 3	$[BMIm]NTf_2$	94[c]
8	LiBr	NFIS 1	$[BMIm]PF_6$	40
9	H_3BO_3	NFIS 1	$[BMIm]PF_6$	20
10	$MnBr_2$	NFIS 1	$[BMIm]PF_6$	58
11	$ZnCl_2$	NFIS 1	$[BMIm]PF_6$	56
12	$Sc(OTf)_3$	NFIS 1	$[BMIm]PF_6$	55
13	$FeCl_3$	NFIS 1	$[BMIm]PF_6$	30
14	$InCl_3$	NFIS 1	$[BMIm]PF_6$	43
15[c]	$MnCl_2{\cdot}4H_2O$	NFIS 1	$[BMIm]PF_6$	96

[a] **3a**: 0.25 mmol; **4a**: 0.3 mmol; NFIS 1: 0.25 mmol; $[BMIm]PF_6$: 100 mg; catalyst: 0.05 mmol.
[b] When organic solvent was used, it was added in a volume of 0.5 mL.
[c] Pure ethyl acetate was used for extracting the product.
[d] Reused in third run.

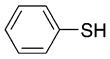
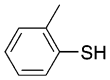
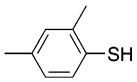
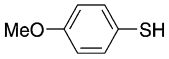
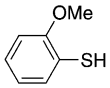
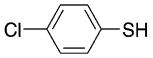
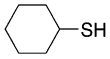
of 95% was obtained under identical conditions (entry 6). It should be noted that, because NFIS 1 is a solid at room temperature, in the absence of $[BMIm]PF_6$, the ionic phase tended to solidify during the extraction of product, making thus the extraction problematic. Therefore, a small amount of $[BMIm]PF_6$ was added for the purpose of facilitating isolation of the product. Because the PF_6 anion is rather unstable in the presence of water, therefore the promoting effect might have resulted from the generation of HF. To clarify this point, a combination of NFIS 3 and $[BMIm]NTf_2$ was also examined, and in this case, the reaction proceeded very well (entry 7). Because the NTf_2 anion was considered as a stable species toward water, the possible influence of the hydrolysis of PF_6 anion on the reaction has thus been excluded. Under identical conditions, many other catalysts, such as LiBr, H_3BO_3, $MnBr_2$, $ZnCl_2$, $Sc(OTf)_3$, $FeCl_3$, and $InCl_3$, were also examined. However, the yields obtained are much lower than that with manganese chloride tetrahydrate (entries 8 to 14). Therefore, $MnCl_2{\cdot}4H_2O$/(NFIS 1+$[BMIm]PF_6$) was proven to be an optimal system for the model reaction in Table 3. All these results demonstrate that the nitro-functionalized imidazolium salt is not only able to replace nitromethane in this acid-catalyzed reaction, but is also capable of enhancing, to some extent, the catalytic activity of $MnCl_2{\cdot}4H_2O$, rendering eventually the model reaction to proceed toward completion.

Because the ionic phase, NFIS 1+$[BMIm]PF_6$, is immiscible with most of the non-polar organic solvents, we are thus able to extract, at the end of the reaction, the formed organic products with a mixture of *n*-heptane and ethyl acetate (v/v = 5/1). This procedure not only allows an easy isolation of the products but also facilitates recycling of the ionic phase, wherein the metal catalyst is immobilized. As shown in Table 3, the recovered ionic liquid as well as the manganese chloride catalyst can be reused at least three times without significant loss of activity (entry 15). Table 4 gives also the results of manganese chloride tetrahydrate-catalyzed ring-opening reactions of **3a**-type dihydropyrans with thiophenols or thiols in NFIS 1/$[BMIm]PF_6$. In some cases, $MnBr_2$ was used in order to improve the reaction yields. As expected, this system has proved to be very effective for these ring-opening reactions, and generally, good to excellent yields could be obtained. Thus, with this type of ring-opening reaction, the capacity of the nitro-func-

Table 4. Substrate scope of manganese(II) halide-catalyzed ring-opening reactions of dihydropyrane with thiols or thiophenols.[a]



3a: $R^1 = R^2 = OMe$;
3b: $R^1 = OMe$, $R^2 = OEt$;
3c: $R^1 = Me$, $R^2 = OEt$;
3d: $R^1 = t\text{-Bu}$, $R^2 = OEt$.

Entry	Catalyst	Dihydropyran	RSH		Product	Yield [%]
1	$MnBr_2$	**3a**		**4b**	**5b**	98
2	$MnCl_2{\cdot}4H_2O$	**3a**		**4c**	**5c**	95
3	$MnCl_2{\cdot}4H_2O$	**3a**		**4d**	**5d**	85
4	$MnCl_2{\cdot}4H_2O$	**3a**		**4e**	**5e**	83
5	$MnCl_2{\cdot}4H_2O$	**3a**		**4f**	**5f**	84
6	$MnBr_2$	**3a**		**4g**	**5g**	98
7	$MnCl_2{\cdot}4H_2O$	**3a**		**4h**	**5h**	71
8	$MnBr_2$	**3b**	**4b**		**5i**	77
9	$MnBr_2$	**3c**	**4b**		**5j**	84
10[b]	$MnBr_2$	**3d**	**4b**		**5k**	76

[a] Dihydropyran: 0.25 mmol, thiols or thiophenols: 0.3 mmol, catalyst: 0.05 mmol, NFIS 1: 0.25 mmol, $[BMIm]PF_6$: 100 mg.
[b] 100 °C, 24 h.

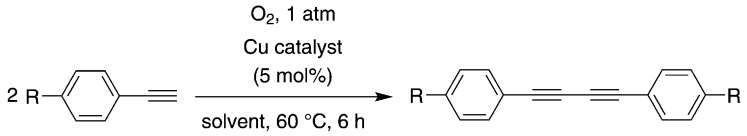
tionalized imidazolium salt for assisting acid catalysis was successfully demonstrated.

The good capacity of the nitro-functionalized imidazolium salts encourages us to further use them in transition metal-catalyzed reactions. The Glaser oxidative homo-coupling reaction of terminal alkynes is an important organic transformation that can produce, in a direct way, diyne derivatives, which are very useful building blocks in organic synthesis.[12] In the past five years, a plethora of methods has flourished around Glaser coupling reactions by using Cu species as catalyst.[13] Generally, in this type of reaction, solid catalysts showed not only a good performance but also, in some cases, a robust activity during the catalyst recycling. Unfortunately, the costs of many solid catalysts are generally high, and thus restrict its application in practical synthesis. On the contrary, many homogeneous Cu catalysts are very cheap, but often suffer from inefficiency in recycling the catalyst and dealing with toxic bases or ligands. Therefore, a new system that can combine both advantages of homogeneous and heterogeneous systems is appealingly needed.

A literature survey also stated that, for Glaser oxidative homo-coupling reactions of alkynes, Cu(I) was used in the most cases, whereas Cu(II) has been rarely investigated,[14] probably because of its low activity. In view of the fact that: (i) Cu(II) salts are generally cheaper than Cu(I) salts, and (ii) Cu(II) salts are more stable than the other salts, we focused our attention on investigating Glaser oxidative homo-coupling reactions of alkyne with Cu(II) salts.

As shown in Table 5, the oxidative coupling of phenylacetylene (**6a**) was investigated using $Cu(OAc)_2$ as catalyst in different solvent systems. In the absence of $Cu(OAc)_2$, no product was detected (entry 1). The catalytic activities of $Cu(OAc)_2$ are rather poor in ionic liquids, such as $[BMIm]PF_6$, $[BMIm]BF_4$, and [BMIm]Cl (entries 2 to 4). Interestingly, in $[BMIm]PF_6$, when $Cu(OAc)_2$ was used in conjunction with a tertiary amine-functionalized ionic liquid, AFIL 1, the yield of **7a** could be increased to 47%

Table 5. Glaser coupling of phenylacetylene in different conditions.[a]



6a: R = H;
6b: R = Me;
6c: R = Bu^n;
6d: R = OMe;
6e: R = F.

7a – 7e

Entry	Alkyne	Cu catalyst	Solvent	Additive (10 mol%)	Product	Yield [%]
1	**6a**	–	[BMIm]PF_6	–	**7a**	0
2	**6a**	$Cu(OAc)_2$	[BMIm]PF_6	–	**7a**	trace
3	**6a**	$Cu(OAc)_2$	[BMIm]BF_4	–	**7a**	trace
4	**6a**	$Cu(OAc)_2$	[BMIm]Cl	–	**7a**	trace
5	**6a**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1	**7a**	47
6	**6a**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 2	**7a**	trace
7	**6a**	$Cu(OAc)_2$	[BMIm]PF_6	triethylamine	**7a**	22
8	**6a**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1 + nitrobenzene	**7a**	89
9	**6a**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1 + nitromethane	**7a**	79
10	***6a***	***$Cu(OAc)_2$***	***[BMIm]PF_6***	***AFIL 1 + NFIS 1***	***7a***	***93***
11	**6a**	$CuCl_2$	[BMIm]PF_6	AFIL 1 + NFIS 1	**7a**	46
12	**6a**	$CuSO_4$	[BMIm]PF_6	AFIL 1 + NFIS 1	**7a**	trace
13	**6a**	CuCl	[BMIm]PF_6	AFIL 1 + NFIS 1	**7a**	71
14	**6a**	CuBr	[BMIm]PF_6	AFIL 1 + NFIS 1	**7a**	51
15	**6a**	CuI	[BMIm]PF_6	AFIL 1 + NFIS 1	**7a**	63
16[b]	**6a**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1 + NFIS 1	**7a**	20
17[c]	**6a**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1 + NFIS 1	**7a**	31
18[d]	**6a**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1 + NFIS 1	**7a**	50
19[e]	***6a***	***$Cu(OAc)_2$***	***[BMIm]PF_6***	***AFIL 1 + NFIS 1***	***7a***	***99***
20	**6b**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1 + NFIS 1	**7b**	99
21	**6c**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1 + NFIS 1	**7c**	97
22	**6d**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1 + NFIS 1	**7d**	93
23	**6e**	$Cu(OAc)_2$	[BMIm]PF_6	AFIL 1 + NFIS 1	**7e**	98

[a] Phenylacetylene, 1.0 mmol; Cu catalyst, 0.025 mmol; solvent, 0.5 mL; additive, 0.1 mmol for each component.
[b] 25 °C.
[c] $Cu(OAc)_2$, 2.0 mol%.
[d] Reaction time, 3 h.
[e] $Cu(OAc)_2$, 10 mol%.

(entry 5). Interestingly, when AFIL 2, that has a methyl group in the C-2 position of the imidazolium ring, was used instead of AFIL 1, only traces of **7a** were obtained (entry 6). Furthermore, a poor yield was also obtained when triethylamine was used in conjunction with [BMIm]PF_6 under identical conditions (entry 7). These results indicates that both the 1,3-dialkyl-2*H*-imidazolium cation and the diethylamino group are important for improving the catalytic activity of $Cu(OAc)_2$.

In order to further improve the catalytic acitivty of $Cu(OAc)_2$ in the model reaction of Table 5, we then turned to search for a suitable co-catalyst. We found unexpectedly that nitro-containing compounds, such as nitrobenzene and nitromethane, exhibited a significant promoting effect on the $Cu(OAc)_2$-catalyzed Glaser coupling reaction in this ionic phase, and the yield of **7a** could be increased to 89% and 79%, respectively (entries 8 and 9). Inspired by these promising results, we then replaced the nitro-containing compounds by a nitro-functionalized imidazolium salt, NFIS 1. As expected, the nitro-functionalized imidazolium salt showed a significant synergistic promoting effect with the tertiary amine-functionalized ionic liquid, AFIL 1, in the model Glaser reaction, and finally, the reaction yield reached 93% (entry 10).

In a later study, other Cu salts, such as $CuCl_2$, $CuSO_4$, CuCl, CuBr, and CuI, were examined in the optimal ternary ionic system composed of [BMIm]PF_6, AFIL 1, and NFIS 1, but the yields obtained were rather poor (entries 11 to 15). These results imply that $Cu(OAc)_2$ has a unique ability to catalyze the model reaction in this three-component ionic phase system. Further investigations revealed

that the reaction was also affected by the temperature, catalyst amount, and reaction time, and the optimal condition are 60 °C, 5 mol% of catalyst, and 6 h of reaction (entries 16 to 18).

The aim of this study is to develop a new catalyst system that not only is capable of catalyzing Glaser coupling reactions efficiently, but also could be recycled easily and steadily. We therefore investigated the recyclability of this system. During the condition optimization, we found that the desired product, **7a**, could be formed quantitatively in the presence of 10 mol% of $Cu(OAc)_2$ (Table 5, entry 19). The quantitative transformation allowed us to isolate the product with a very simple procedure. After the reaction, the system was extracted repeatedly with *n*-heptane until the upper organic phase showed no strong UV response. The product could be obtained by following distillation of the combined organic phases (Figure 2). Further analysis of the product with ^{1}H NMR revealed that no detectable contamination of the imidazolium salt could be observed, indicating the good performance of this isolation method. This procedure not only avoids the use of silica gel column chromatography for the product isolation, but also allows an easy recovery of *n*-heptane, thus minimizing the generation of waste. The recovered ionic phase as well as the catalyst could be reused at least five times without any significant loss of the catalytic activity (Figure 3). Furthermore, some other terminal alkynes can also be converted to the corresponding dialkynes in excellent yields by means of this system (Table 5, entries 20 to 23). Therefore, the combination of $Cu(OAc)_2$ with imidazolium salts offers a robust and efficient catalyst system for Glaser coupling reactions. Particularly, the use of a nitro-functionalized imidazolium salt is pivotal for enhancing the catalyst system to be efficient

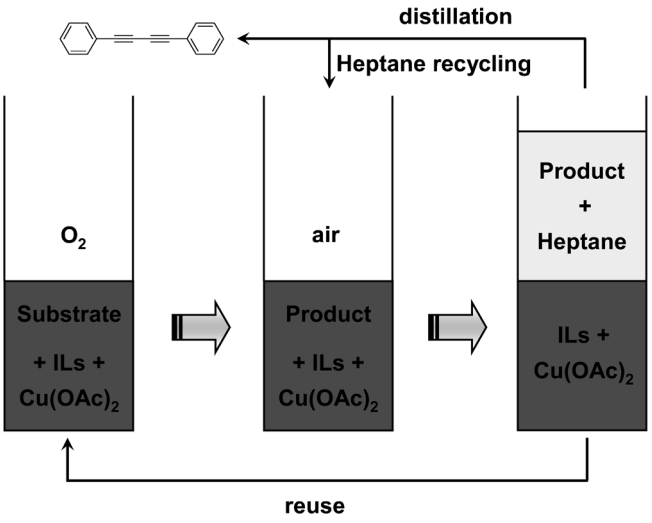


Figure 2. Recycling procedure of $Cu(OAc)_2$/ionic phase system.

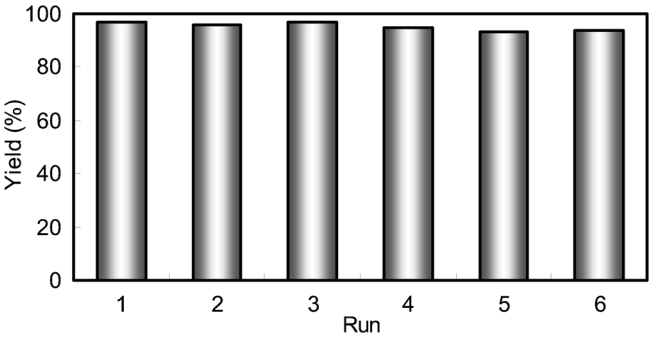


Figure 3. Reuse of the $Cu(OAc)_2$/ionic liquid system.

and recyclable. By means of these promising results, the nitro-functionalized imidazolium salt was demonstrated again to be a useful reagent for transition metal-catalyzed organic reactions.

Although we cannot yet offer an explanation for the high activity of $Cu(OAc)_2$ in the ionic phase, the good performance might be related to a synergistic interaction of AFIL 1, Cu(II), and NFIS 1. In view of the fact that replacing AFIL 1 by AFIL 2, which contains a methyl group in the C-2 position of the imidazolium ring, resulted in a dramatic decrease of the reaction yield, it is thus not unreasonable to expect that a carbene fragment, which could be generated from the 1,3-dialkyl-2*H*-imidazolium salt, might be involved in the catalytic cycle. In addition, because of the following reasons: (i) $Cu(OAc)_2$ catalyst does not work in a normal ionic liquid, $[BMIm]PF_6$ in the absence of AFIL 1; and (ii) the NFIS 1/AFIL 1 system could be reused steadily although AFIL 1 was used in catalytic amounts, the diethylamino group in AFIL 1 does not seem to work as a base that the conventional $Cu(OAc)_2$ catalyst systems needed.[14] Therefore, we suspect that the diethylamino group can play a key role in constructing a catalytically active species.

Shreeve and co-workers have reported a catalyst system for the oxidative coupling of terminal alkynes, in which a tertiary amine-functionalized imidazolium ionic liquid was used in conjunction with a $PdCl_2(PPh_3)_2$ catalyst.[15] Unfortunately, no synergistic effect of the tertiary amine group and the imidazolium ring was observed in Shreeve's system. But, a palladium-carbene complex (**I**) that was prepared by using a 1-butyl-3-methylimidazolium salt as precursor and a triphenylphosphine as an additional ligand has been reported by Ryu and Nokihara, to be catalytically active for many C–C coupling reactions, such as Suzuki, Stille, Sonogashira, and Heck reactions.[16] It should be noted that preparation of (**I**) is quite easy, and can be performed under mild conditions. An organic base, diisopropylamine, was sufficient for the removal of the proton in the C-2 position of the imidazolium ring.[16(a)] Inspired by these results, and taking into consideration the significant effect of both the

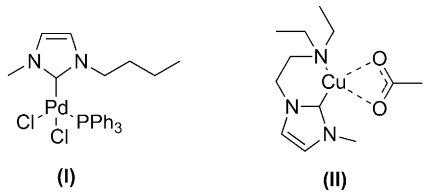


Figure 4. Possible Cu species for catalyzing the Glaser coupling of **6a**.

1,3-dialkyl-2*H*-imidazolium ring and the diethylamino group on the catalytic activity of $Cu(OAc)_2$, we thus proposed a possible structure of the catalytic active species as shown in Figure 4. Under the reaction conditions, a carbene fragment might be somehow formed. Because of the presence of a tertiary amino group, the newly formed species might act as a chelating NHC-N donor hybrid ligand[17] to coordinate with the copper ion center, generating the Cu-carbene complex (**II**) that might possess a moderate activity for catalyzing the model Glaser coupling reaction. It should be noted that coordination of the diethylamino group to a metal center can form a six-membered ring that might allow an easy construction of the intermediate (**II**). In fact, such a coordination of a nitrogen donor-functionalized carbene to a metal center, rhodium, has been reported to be possible by Herrmann.[18] It should be noted also that, although our hypothesis seems to be viable for explaining the synergistic effect of 1,3-dialkyl-2*H*-imidazolium salt and the diethylamino group for the $Cu(OAc)_2$ catalyst, the exact reason of why NFIS 1 could significantly improve the catalytic activity is still unclear. Futhermore, because we are failed to obtain supportive data by using ESI-MS, the mechanism still remains to be delineated in detail. We are now actively pursuing on investigating the mechanism of these catalysis.

Conclusions

In conclusion, nitro-functionalized imidazolium salts were proven to be environmentally benign alternatives to nitromethane that is a volatile, explosive, and widely used organic solvent. Three reactions including the trimethylsilylation of alcohols with HMDS, the ring-opening reaction of 2-aryl-3,4-dihydropyrans with thiophenols or thiols, and a copper-mediated oxidative coupling of alkynes, were examined, and in all these reactions, the nitro-functionalized imidazolium salts proved to be not only capable of replacing nitromethane but are also profitable for the selected model reactions. For example, the yields of the trimethylsilylation of alcohols with HMDS over NFIS 1 are competitive with that obtained by using nitromethane as solvent but NFIS 1 was used in only catalytic amounts. The catalytic activity of manganese chloride tetrahydrate for the ring-opening of dihydropyran **3a** with thiophenol could be significantly improved in relation to its counterpart deriving from the nitromethane system. An unexpected subtle synergistic promoting effect of NFIS 1 and AFIL 1 was also observed in $Cu(OAc)_2$-catalyzed oxidative coupling of phenylacetylene. In all the reactions studied, the imidazolium salt along with the metal catalyst, if involved, could be easily recovered and reused without significant loss of activity. The simple procedures for their preparation as well as the easy recovery and reuse of these novel materials are expected to contribute to the development of more benign systems for organic synthesis and catalysis.

Experimental Section

All chemicals were used as received. All reactions were conducted in a 10-mL V-type flask equipped with triangle magnetic stirring. In a typical silylation reaction, NFIS 1 (0.05 mmol) was mixed with benzyl alcohol (0.5 mmol) and HMDS (0.5 mmol) under air. The mixture was stirred for 1 h at room temperature. After reaction, the mixture was mixed with a mixture of ethyl acetate and *n*-heptane (v/v = 1/5, 2.0 mL). The upper organic solution was then loaded onto a preparative TLC plate. The product **2a** was obtained in a yield of 99%.

The other reactions were performed as an analogous procedure, and the details are available in the electronic Supporting Information.

For the reuse experiment, the reaction scale was increased to 20.0-mmol. After the reaction, NFIS 1 was filtered off and washed with *n*-heptane (4 mL × 3). The recovered NFIS 1 was directly submitted to the next run after drying at room temperature for 12 h. The product **2a** was isolated through silica column chromatography by using a solution composed of ethyl acetate and *n*-heptane (v/v = 1/10) as eluting solvent.

Spectroscopic Data of the New Compounds

1,2-Dimethyl-3-(4-nitrobenzyl)imidazolium hexafluorophosphate (NFIS 4): Colorless solid; mp 170–172 °C; ^{1}H NMR [$(CD_3)_2SO$]: $\delta = 2.57$ (s, 3H), 3.77 (s, 3H), 5.60 (s, 2H), 7.56 (d, $J = 7.2$ Hz, 2H), 7.72 (dd, $J_a = 2.0$ Hz, $J_b = 14.0$ Hz,2H), 8.26 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR: $\delta = 9.5$, 30.7, 35.0, 49.9, 121.4, 123.0, 124.0, 128.9, 142.1, 145.2, 147.5; IR: $\nu = 3164$, 3084, 2995, 2972, 2859, 1601, 1523, 1450, 1418, 1388, 1349, 1293, 1275, 1190, 1168, 1115, 1083, 1046, 1017, 976, 951, 848, 833, 782, 736, 679, 646, 631, 558 cm^{-1}; HR-MS (ESI): $m/z =$ 232.1089, calcd. for $C_{12}H_{14}N_3O_2$ $[M]^+$: 232.1086 (cation part of salt).

(3,4-Dimethoxyphenethoxy)trimethylsilane (2e): Yellow pale liquid; ^{1}H NMR ($CDCl_3$): $\delta = 0.15$ (s, 9H), 2.84 (t, $J =$ 6.8 Hz, 2H), 3.83 (t, $J = 7.2$ Hz, 2H), 3.83 (s, 3H), 3.92 (s, 3H), 6.79–6.86 (m, 3H); ^{13}C NMR: $\delta = 0.5$, 39.0, 55.7, 55.8, 64.0, 111.1, 112.4, 120.9, 131.6, 147.4, 148.7; IR: $\nu = 3539$, 2998, 2953, 2909, 2835, 2736, 1727, 1591, 1515, 1464, 1417, 1334, 1261, 1156, 1141, 1091, 1031, 930, 876, 842, 807, 759,

759, 690, 632 cm^{-1} ; HR-MS (ESI): $m/z=277.1228$, calcd. for $C_{13}H_{22}NaO_3Si$ $[M+Na]^+$: 277.1236.

1-[2-(Trimethylsilyloxy)ethyl]-1*H*-indole (2m): Yellow liquid; ^1H NMR ($CDCl_3$): $\delta=0.15$(m, 9H), 4.02 (t, $J=5.6$ Hz, 2H), 4.35 (t, $J=5.2$ Hz, 2H), 6.67 (d, $J=2.0$ Hz, 1H), 7.27–7.33 (m, 2H), 7.37–7.39 (m, 1H), 7.50 (t, $J=7.6$ Hz, 1H), 7.80 (d, $J=6.8$ Hz, 1H); ^{13}CNMR: $\delta=-0.6$, 48.6, 48.7, 61.8, 101.2, 101.6, 109.5, 119.4, 119.7, 121.0, 121.2, 121.5, 121.8, 128.7, 128.8, 136.3; IR: $\nu=3407$, 3054, 2957, 2870, 1612, 1512, 1463, 1399, 1359, 1334, 1315, 1252, 1200, 1111, 1077, 1013, 922, 843, 741, 718, 691, 612 cm^{-1}; HR-MS (ESI): $m/z=256.1126$, calcd. for $C_{13}H_{19}NNaOSi$ $[M+Na]^+$: 256.1134.

2-[(Trimethylsilyloxy)methyl]-1*H*-indole (2n): Brown solid; mp 68–70 °C; ^1H NMR ($CDCl_3$): $\delta=0.21$ (s, 9H), 4.77–4.87 (m, 2H), 6.39 (s, 1H), 7.21–7.26 (m, 2H), 7.36 (d, $J=8.0$ Hz, 1H), 7.61 (d, $J=7.6$ Hz, 1H), 8.46 (s, 1H); ^{13}C NMR: $\delta=-0.4$, 58.6, 99.5, 100.5, 110.9, 119.8, 120.5, 121.8, 128.1, 128.4, 136.1, 136.4, 137.7, 137.8; IR: $\nu=3394$, 3375, 3056, 2959, 2937, 1456, 1428, 1369, 1342, 1290, 1250, 1219, 1136, 1052, 970, 926, 843, 796, 753, 736, 705, 630, 609, 533 cm^{-1}; HR-MS (ESI): $m/z=242.0969$, calcd. for $C_{12}H_{17}NNaOSi$ $[M+Na]^+$: 242.0977.

Ethyl 2-[(4-methoxyphenyl)(trimethylsilyloxy)methyl]-acrylate (2p): Yellow liquid; ^1H NMR ($CDCl_3$): $\delta=0.15$ (s, 9H), 1.29 (t, $J=6.4$ Hz, 3H), 3.84 (s, 3H), 4.20 (q, $J=6.8$ Hz, 2H), 5.68 (s, 1H), 6.08 (t, $J=1.6$ Hz, 1H), 6.35 (s, 1H), 6.91 (d, $J=8.8$ Hz, 2H), 7.33–7.36(m, 2H); ^{13}C NMR: $\delta=0.0$, 14.1, 55.1, 60.5, 72.2, 76.8, 77.2, 77.5, 113.5, 123.5, 128.4, 134.5, 144.1, 159.0, 166.0; IR: $\nu=2958$, 2904, 2837, 1719, 1612, 1511, 1464, 1371, 1299, 1251, 1173, 1146, 1075, 1036, 960, 888, 960, 753, 688, 661, 615, 545 cm^{-1}; HR-MS (ESI): $m/z=331.1338$, calcd. for $C_{16}H_{24}NaO_4Si$ $[M+Na]^+$: 331.1342.

Methyl 2-acetyl-5-[(3,5-dimethylphenyl)thio]-5-(4-methoxyphenyl)pentanoate (5a): Mixture of diastereomers; yellow liquid; ^1H NMR ($CDCl_3$): $\delta=1.73$–1.83 (m, 4H), 2.05 (s, 1.5H), 2.06 (s, 1.5H), 2.15 (s, 6H), 3.27–3.32 (m, 1H), 3.60 (s, 3H), 3.70 (s, 3H), 4.00–4.05 (m, 1H), 6.73 (d, $J=8.8$ Hz, 3H), 6.79 (s, 2H), 7.06 (d, $J=8.8$ Hz, 2H); ^{13}C NMR: $\delta=21.3$, 26.3, 26.4, 28.8, 28.9, 33.8, 33.9, 52.4, 52.5, 55.4, 59.2, 59.3, 114.0, 128.9, 129.0, 129.1 , 130.0 ,130.1, 133.3, 133.4, 134.3, 134.4, 138.3, 158.9, 170.0, 170.1, 202.8; IR: $\nu=3028$, 2954, 2917, 2837, 1741, 1713, 1646, 1606, 1581, 1509, 1454, 1437, 1357, 1301,1247, 1174, 1144, 1110, 1088, 1031, 914, 884, 832, 799, 737, 687, 631, 580 cm^{-1}; HR-MS (ESI): $m/z=423.1591$, calcd. for $C_{23}H_{28}NaO_4S$ $[M+Na]^+$ 423.1606.

Methyl 2-acetyl-5-(4-methoxyphenyl)-5-(phenylthio)pentanoate (5b): Mixture of diastereomers; yellow liquid; ^1H NMR ($CDCl_3$): $\delta=1.85$–1.91 (m, 4H), 2.13 (s, 1.5H), 2.14 (s, 1.5H), 3.35–3.40 (m, 1H), 3.67 (s, 1.5H), 3.67 (s, 1.5H), 3.76 (s, 3H), 4.06–4.10 (m, 1H), 6.79 (d, $J=8.4$ Hz, 2H), 7.13 (d, $J=8.8$ Hz, 2H), 7.18–7.26 (m, 5H); ^{13}C NMR: $\delta=26.2$, 26.3, 28.8, 28.9, 33.7, 33.9, 52.5, 52.6, 52.7, 55.3, 59.1, 59.2, 113.9, 127.2, 127.3, 128.7, 128.8, 132.5, 132.6, 133.1, 134.7, 158.8, 169.9, 167.0, 202.7; IR: $\nu=3057$, 3001, 2953, 2837, 1742, 1715, 1647, 1609, 1582, 1511, 1438, 1358, 1302, 1249, 1177, 1147, 1112, 1032, 892, 835, 743, 693, 611, 558 cm^{-1}; HR-MS (ESI): $m/z=395.1288$, calcd. for $C_{21}H_{24}NaO_4S$ $[M+Na]^+$: 395.1293.

Methyl 2-acetyl-5-(4-methoxyphenyl)-5-(*o*-tolylthio)pentanoate (5c): Mixture of diastereomers; yellow liquid; ^1H NMR ($CDCl_3$): $\delta=1.82$–1.94 (m, 4H), 2.13 (s, 1.5H), 2.14 (s, 1.5H), 2.29 (s, 3H), 3.38 (m, 1H), 3.68 (s, 1.5H), 3.68 (s, 1.5H), 3.76 (s, 3H), 4.02–4.06 (m, 1H), 6.78 (d, $J=8.8$ Hz, 2H), 7.10–7.15 (m, 5H), 7.22–7.26 (m, 1H); ^{13}C NMR: $\delta=20.8$, 26.3, 26.4, 28.9, 29.0, 33.9, 34.0, 51.9, 52.0, 52.5, 52.6, 55.3, 59.2, 59.3, 114.0, 126.3, 127.2, 127.3, 128.8, 130.3, 132.6, 132.7, 133.1, 133.2 ,134.1, 134.2, 140.0, 140.1, 158.9, 170.0, 170.1, 202.7; IR: $\nu=3058$, 3003, 2952, 2838, 1740, 1713, 1608, 1510, 1459, 1438, 1357, 1300, 1247, 1175, 1147, 1112, 1062, 1032, 989, 913, 835, 746, 680, 545 cm^{-1}; HR-MS (ESI): $m/z=409.1437$, calcd. for $C_{22}H_{26}NaO_4S$ $[M+Na]^+$: 409.1449.

Methyl 2-acetyl-5-[(2,4-dimethylphenyl)thio]-5-(4-methoxyphenyl)pentanoate (5d): Mixture of diastereomers; yellow liquid; ^1H NMR ($CDCl_3$): $\delta=1.79$–1.86 (m, 2H), 1.88–1.94 (m, 2H), 2.13 (s, 1.5H), 2.14 (s, 1.5H), 2.25 (s, 6H), 3.35–3.39 (m, 1H), 3.68 (s, 3H), 3.77 (s, 3H), 3.93–3.97 (m, 1H), 6.78 (d, $J=8.4$ Hz, 2H), 6.86 (d, $J=8.0$ Hz, 1H), 6.96 (s, 1H), 7.09–7.14 (m, 3H); ^{13}C NMR: $\delta=20.8$, 21.2, 26.4, 26.5, 29.0, 33.7, 33.9, 52.4, 52.5, 52.6, 52.7, 55.4, 59.3, 59.4, 114.0, 127.2, 128.8, 130.4, 130.5, 131.2, 133.5, 133.8, 133.9, 137.5, 137.6, 140.6, 140.7, 158.9, 170.1, 170.2, 202.8; IR: $\nu=3000$, 2952, 2932, 2837, 1741, 1715, 1647, 1608, 1510, 1438, 1357, 1301, 1248, 1176, 1145, 1112, 1033, 879, 814, 763, 722, 687, 664, 630 cm^{-1}; HR-MS (ESI): $m/z=423.1592$, calcd. for $C_{23}H_{28}NaO_4S$ $[M+Na]^+$: 423.1606.

Methyl 2-acetyl-5-(4-methoxyphenyl)-5-[(4-methoxyphenyl)thio]pentanoate (5e): Mixture of diastereomers, yellow liquid; ^1H NMR ($CDCl_3$): $\delta=1.77$–1.93 (m, 4H), 2.14 (s, 1.5H), 2.15 (s, 1.5H), 3.35–3.40 (m, 1H), 3.69 (s, 1.5H), 3.69 (s, 1.5H), 3.76 (s, 1.5H), 3.76 (s, 1.5H),3.77 (s, 1H), 3.88–3.92 (m, 1H), 6.72 (d, $J=0.8$ Hz, 1H), 6.75 (d, $J=0.8$ Hz, 1H), 6.77 (s, 1H), 6.79 (d, $J=0.8$ Hz, 1H), 7.04 (d, $J=8.8$ Hz, 2H), 7.14 (d, $J=2.4$ Hz, 1H), 7.16 (d, $J=2.4$ Hz, 1H); ^{13}C NMR: $\delta=26.3$, 26.4, 28.8, 28.9, 33.3, 33.4, 52.5, 52.6, 53.8, 53.9, 55.3, 55.4, 59.2, 59.3, 113.8, 113.9, 114.3, 128.9, 136.2, 158.8, 159.7, 170.0, 170.1, 202.8; IR: $\nu=3062$, 3001, 2953, 2837, 1742, 1715, 1645, 1593, 1508, 1495, 1459, 1441, 1358, 1284, 1247, 1176, 1150, 1109, 1080, 991, 913, 888, 830, 800, 736, 698, 641, 609, 527, 503 cm^{-1}; HR-MS (ESI): $m/z=425.1397$, calcd. for $C_{22}H_{26}NaO_5S$ $[M+Na]^+$: 425.1399.

Methyl 2-acetyl-5-(4-methoxyphenyl)-5-[(2-methoxyphenyl)thio]pentanoate (5f): Mixture of diastereomers; yellow liquid; ^1H NMR ($CDCl_3$): $\delta=1.82$–1.91 (m, 4H), 2.13 (s, 1.5H), 2.14 (s, 1.5H), 3.37–3.40 (m, 1H), 3.67 (s, 1.5H), 3.67 (s, 1.5H), 3.74 (s, 3H), 3.85 (s, 3H), 4.22–4.29 (m, 1H), 6.76–6.81 (m, 4H), 7.14–7.18 (m, 4H); ^{13}C NMR: $\delta=26.3$, 26.4, 28.8, 33.8, 33.9, 50.1, 50.2, 52.5, 55.3, 55.8, 59.2, 110.7, 113.8, 120.8, 122.7, 128.7, 128.8, 133.6, 133.7, 158.7, 169.9, 170.0, 202.8; IR: $\nu=3061$, 3002, 2953, 2837, 1742, 1715, 1647, 1609, 1580, 1511, 1472, 1435, 1358, 1300, 1272, 1246, 1177, 1149, 1111, 1071, 1026, 913, 836, 797, 753, 685, 648, 632, 611, 538 cm^{-1}; HR-MS (ESI): $m/z=425.1392$, calcd. for $C_{22}H_{26}NaO_5S$ $[M+Na]^+$: 425.1399.

Methyl 2-acetyl-5-[(4-chlorophenyl)thio]-5-(4-methoxyphenyl)pentanoate (5g): Mixture of diastereomers; yellow liquid; ^1H NMR ($CDCl_3$): $\delta=1.81$–1.92 (m, 4H), 2.15 (s, 1.5H), 2.16 (s, 1.5H), 3.35–3.40 (m, 1H),3.69 (s, 1.5H), 3.69 (s, 1.5H), 3.77 (s, 3H), 4.01–4.05 (m, 1H), 6.78 (d, $J=8.4$ Hz, 2H), 7.09 (d, $J=8.4$ Hz, 2H), 7.11–7.17 (m, 4H);

^{13}C NMR: δ = 26.2, 26.3, 28.9, 29.0, 33.7, 33.8 ,52.6, 52.7, 53.0, 53.1, 55.4, 59.2, 59.3, 114.0, 128.9, 129.0, 132.8, 132.9, 133.1, 133.2, 133.5, 133.6, 134.1, 134.2, 159.0, 169.9, 170.0, 202.6; IR: ν = 3001, 2953, 2919, 1739, 1713, 1648, 1609, 1509, 1471, 1437, 1386, 1356, 1301, 1245, 1176, 1148, 1092, 1033, 1012, 960, 903, 881, 819, 775, 743, 678, 630, 595 cm^{-1}; HR-MS (ESI): m/z = 429.0900, calcd. for $C_{21}H_{23}ClNaO_4S$ $[M+Na]^+$: 429.0903.

Methyl 2-acetyl-5-(cyclohexylthio)-5-(4-methoxyphenyl)-pentanoate (5h): Mixture of diastereomers; yellow liquid; ^{1}H NMR ($CDCl_3$): δ = 1.67–1.71 (m, 5H), 1.72 (s, 1H), 1.74–1.85 (m, 8H), 1.87 (s, 1.5H), 1.88 (s, 1.5H), 1.94–2.04 (m, 1H), 3.36–3.41 (m, 1H), 3.70 (s, 1.5H), 3.71 (s, 1.5H), 3.78 (m, 4H), 6.83 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 25.8, 25.9, 26.1, 26.4, 28.8, 28.9, 33.2, 33.3, 33.9, 34.7, 34.8, 42.5, 42.6, 47.1, 47.2, 52.4, 52.5, 55.3, 59.3, 59.4, 113.9, 128.6, 128.7, 134.6, 158.6, 170.0, 170.1, 202.8, 202.9; IR: ν = 3027, 3000, 2929, 2852, 1743, 1716, 1610, 1510, 1446, 1358, 1302, 1248, 1176, 1148, 1110, 1035, 998, 834, 744, 694, 610, 592, 553, 539 cm^{-1}; HR-MS (ESI): m/z = 401.1757, calcd. for $C_{21}H_{30}NaO_4S$ $[M+Na]^+$: 401.1762.

Ethyl 2-acetyl-5-(4-methoxyphenyl)-5-(phenylthio)pentanoate (5i): Mixture of diastereomers; colorless liquid; ^{1}H NMR ($CDCl_3$): δ = 1.21 (dt, J_a = 2.8 Hz, J_b = 7.2 Hz, 3H), 1.72–1.97 (m, 4H), 2.12 (s, 1.5H), 2.13 (s, 1.5H), 3.34 (q, J = 6.0 Hz, 1H), 3.75 (s, 3H), 4.06–4.18 (m, 3H), 6.78 (td, J_a = 2.4 Hz, J_b = 8.8 Hz, 2H), 7.13 (dd, J_a = 1.6 Hz, J_b = 8.8 Hz, 2H), 7.16–7.22 (m, 3H), 7.22–7.28 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.1, 26.1, 26.2, 28.8, 28.8, 33.7, 33.8, 52.6, 52.6, 55.2, 59.3, 59.4, 61.5, 113.9, 127.2, 127.2, 128.7, 128.8, 132.5, 132.5, 133.1, 133.2, 134.7, 134.8, 158.8, 169.4, 169.5, 202.7; IR: ν = 3060, 2960, 2937, 2837, 1738, 1716, 1608, 1510, 1454, 1360, 1303, 1249, 1176, 1035, 835, 744, 692 cm^{-1}; HR-MS (ESI): m/z = 409.1444, calcd. for $C_{22}H_{26}NaO_4S$ $[M+Na]^+$: 409.1449.

Ethyl 2-acetyl-5-(phenylthio)-5-(p-tolyl)pentanoate (5j): Mixture of diastereomers; colorless liquid; ^{1}H NMR ($CDCl_3$): δ = 1.22 (dt, J_a = 2.0 Hz, J_b = 7.2 Hz, 3H), 1.73–1.97 (m, 4H), 2.13 (s, 1.5H), 2.14 (s, 1.5H), 2.29 (s, 3H), 3.34 (q, J = 6.4 Hz, 1H), 4.06–4.18 (m, 3H), 7.06 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.15–7.22 (m, 3H), 7.23–7.28 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.1, 21.1, 26.1, 26.2, 28.7, 28.8, 33.7, 33.8, 52.9, 53.0, 59.4, 59.4, 61.5, 61.5, 127.1, 127.1, 127.6, 128.7, 129.2, 132.3, 132.4, 134.9, 134.9, 137.0, 138.1, 138.2, 169.4, 169.5, 202.7; IR: ν = 3053, 3020, 2980, 2925, 2866, 1738, 1716, 1642, 1583, 1512, 1443, 1359, 1243, 1145, 1023, 821, 742, 692 cm^{-1}; HR-MS (ESI): m/z = 393.1495, calcd. for $C_{22}H_{26}NaO_3S$ $[M+Na]^+$: 393.1500.

Ethyl 2-acetyl-5-[4-(*tert*-butyl)phenyl]-5-(phenylthio)pentanoate (5k): Mixture of diastereomers; colorless liquid; ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, J = 7.2 Hz, 3H), 1.29 (s, 9H), 1.64–2.00 (m, 4H), 2.11 (s, 1.5H), 2.12 (s, 1.5H), 3.34 (q, J = 7.6 Hz, 1H), 4.12 (quint, J = 6.8 Hz, 3H), 7.13–7.22 (m, 5H), 7.23–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 14.1, 26.1, 26.2, 28.7, 28.8, 31.4, 33.7, 33.8, 34.5, 52.8, 52.8, 59.4, 59.5, 61.4, 61.5, 125.5, 127.1, 127.1, 127.4, 128.7, 128.7, 132.0, 132.3, 132.3, 135.0, 135.0, 138.0, 138.0, 150.2, 169.5, 169.5, 202.8; IR: ν = 3056, 2965, 2905, 2869, 1739, 1717, 1643, 1584, 1470, 1362, 1146, 1024, 842, 744, 692, 570 cm^{-1}; HR-MS (ESI): m/z = 435.1964, calcd. for $C_{25}H_{23}NaO_3S$ $[M+Na]^+$: 435.1970.

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