A Novel and Versatile Access to Task-Specific Ionic Liquids Based on 1,2,3-Triazolium Salts

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Abstract: Novel task-specific ionic liquids based on 1,2,3-triazolium salts were prepared in a straightforward two-step procedure. Azides and alkynes were transformed into 1,4-disubstituted 1,2,3-triazoles by Cu-catalyzed click reaction. Subsequent alkylation afforded 1,3,4-trisubstituted 1,2,3-triazoles as ionic liquids. Useful functionalities, such as organocatalysts, fluorophors or linkers can be incorporated into the ionic liquids in this way.

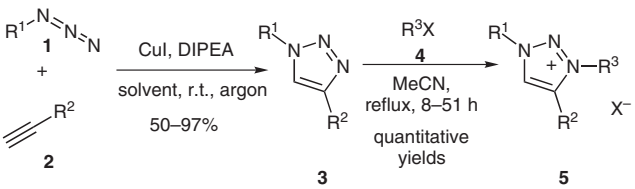
Key words: ionic liquids, alkylation, heterocycles, click reaction, 1,2,3-triazolium salts

Ionic liquids (ILs) are organic salts that are liquids at temperatures below 100 °C. They have gained wide interest and broad application in academia and also in industry.[1–3] ILs can be advantageously used as solvents of low vapor pressure, with special solvent properties within a wide range of polarity and usually of low toxicity. They can often be easily recycled and allow retaining a catalyst for repeated application. Some ionic liquids are considered to be 'green solvents'.[2,4] As a more advanced type of ionic liquids, task-specific ionic liquids (TSILs) have been developed.[5,6] Here, the ionic liquid does not only act as a solvent but at the same time performs a function, often catalytic activity. So far such task-specific ionic liquids were mainly based on imidazolium, pyridinium and ammonium salts, where the functionality was usually linked to the N atom by alkylation, e.g. a chiral, (*S*)-proline-derived pyrrolidin-2-methyl group was covalently bound to an imidazole group and the imidazolium salts obtained by further alkylations could successfully be used in asymmetric Michael additions to nitroolefins.[7] In order to introduce the functionality into the ionic liquids, the functionality has to be furnished with alkylating properties in most cases to allow covalent connection to the N atom.

We report here a versatile novel access to new task-specific ionic liquids which are based on 1,2,3-triazoles obtained by click chemistry. This highly current methodology is based on the reaction of azides **1** with alkynes **2** in the presence of Cu(I) catalysts, which can also be obtained in situ from Cu(II). Since its development in 2002[8,9] numerous applications of this reaction have been reported linking relevant R^1 and R^2 groups together via a 1,2,3-triazole ring.[10–14] The N-alkylation of 1,2,3-triazoles has been known long before the click reaction was invented, when Gompper treated 1,2,3-triazoles obtained by 1,3-dipolar addition with alkylating reagents.[15] The alkylation sometimes results in the formation of regioisomeric 2- and 3-alkyl triazolium salts.[15–17] When soft alkylating reagents were used 1,3-disubstituted products were formed preferentially.

We seek to use this sequence to synthesize trisubstituted 1,2,3-triazolium salts **5** which can be expected to behave like ILs. So far, only 1-amino-3-alkyl-1,2,3-triazolium salts have been reported as ILs in the 1,2,3-triazolium series. These compounds were neither obtained via click chemistry nor used in organic synthesis but rather used as energetic fuel.[18,19] We aimed to give a proof of principle for simple 1,2,3-triazole-based ILs substituted with simple alkyl and benzyl substituents and in particular for the more challenging incorporation of functionalities into the substituents in the 1,2,3-triazole ring. For the present short communication, we chose chiral amines as potential organocatalysts, protected amino groups as possible linkers, and fluorophors as functionalities. As can be seen from Table 1, the functionalities could be incorporated either into the azide **1** or in the alkyne **2** or in both. In most cases high yields of the corresponding 1,4-disubstituted 1,2,3-triazoles **3** were obtained. The products were further alkylated with alkyl iodides or bromides **4** affording the expected 1,3,4-trialkyl-1,2,3-triazolium salts **5** in quantitative yields. All the products **5** (except for **5h**; mp 79–81 °C) appeared as oils or sticky oils at room temperature and thus are ILs. Therefore, salt metathesis in order to lower the melting points was not necessary so far. Clean NMR spectra were obtained for all ILs **5** as well as for their precursors **3**.[20] Mixtures of regioisomers were not observed. The location of the substituent R^3 at position 3 was proved by NOESY investigation showing proximity of the groups R^3 and R^2 in products **5**.

In summary, we have found a straightforward and very versatile access to trisubstituted 1,2,3-triazolium salts as a novel class of ILs by copper-catalyzed click reaction of



Scheme 1

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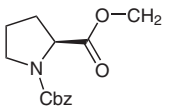
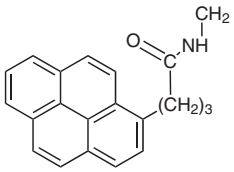
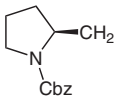
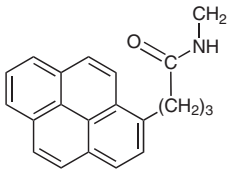
Table 1 1,4-Disubstituted 1,2,3-Triazoles **3** and 1,3,4-Trisubstituted 1,2,3-Triazolium Salts **5**[a]

3/5	R^1	R^2	R^3	X	Solvent	CuI (equiv)	Time (h)	Yield (%) of **3**	Mp (°C) of **3**	**4** (equiv)	Time (h)
a	benzyl	*n*-Bu	Me	I	$CHCl_3$	1.05	3	91	54–55	10	8
b	benzyl	*n*-pentyl	Me	OTs	$CHCl_3$	1.05	72	93	33	1[b]	48
c	4-benzyloxybenzyl	*n*-pentyl	Me	I	MeOH–$CHCl_3$ (2:1)	1.05	77	97	93–95	7	15
d	3-methoxybenzyl	3-phthalimidopropyl	Et	Br	DMF	1.05	36	50	60–62	137[c]	96
e	benzyl		Me	I	$CHCl_3$	1.05	73	96	oil	6	8
f	3-methoxybenzyl		*n*-Pr	I	DMF	1.05	90	81	oil	10	51
g		*n*-pentyl	Me	I	MeOH	5[d]	88	83	oil	28	8
h	3-phthalimidopropyl		Me	I	DMF	1.05	88	59	165–166	28	8

[a] Quantitative yields were obtained for all products **5**, which appeared as sticky oils (except for **5h** which was a solid with mp 79–81 °C).
[b] MeCN (50 mL) was used as solvent.
[c] Because of the low boiling point of EtBr a large excess was used together with the same volume of MeCN as solvent.
[d] The procedure described by Fazio et al.[21] was adopted, but as shown with the other examples, equimolar quantities of CuI were sufficient as well.

azides **1** with alkynes **2**. This methodology allows to link functionalities, such as organocatalytic moieties, fluorophors, reactive groups for further linking and should also be applicable to other functionalities, such as ligands for metal complexes or biomolecules. In principle it should be further possible to link three functionalities via a 1,2,3-triazolium salt, if the alkylating reagent **4** is functionalized as well. Such investigations as well as applications of the novel ILs **5** in organic synthesis are currently underway in our laboratories. We are using the ILs **5** as such or in combination with other cheaper and commercially available IL lacking functional groups. Here, the former provides the functionality and the latter acts as the solvent.

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(20) **Preparation of 3**; **General Procedure**: The azide **1** (20 mmol) was dissolved in the appropriate solvent (50 mL) and CuI (see Table 1) was added. The flask was flushed with argon and the mixture was kept under argon until the workup procedure (balloon) was followed. DIPEA (see Table 1) and the alkyne **2** (10 mmol) were added one after the other, the latter in portions under stirring. If the alkyne was a solid or a sticky liquid, the solvent quantity of 50 mL was shared for dissolving the azide and the alkyne. After a short time an exothermic reaction started and the pace of the addition of the alkyne was adjusted accordingly. Cooling by a water-bath might be advisable. After complete addition of the alkyne stirring was continued at r.t. The mixture was diluted with $CHCl_3$ (50 mL) and filtered. The filtrate was evaporated and the residue was purified by column chromatography (Kieselgel 60; MeOH–$CHCl_3$, 1:19). If DMF was used as solvent, the reaction mixture was diluted with $CHCl_3$ (250 mL), filtered and the filtrate was washed with H_2O (3 × 150 mL) and dried with Na_2SO_4 before volatile compounds were removed under vacuum. Eventually the washing procedure had to be repeated.
Preparation of 5; General Procedure: A solution of the 1,2,3-triazole **3** (20 mL) and the alkylating reagent **4** (see Table 1) in anhyd MeCN (30 mL) was refluxed (see Table 1). All volatile compounds were removed under vacuum with a rotary evaporator leaving behind the ionic liquid as an oil or a sticky oil.
Compound 3a: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 1.32 (sext, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 1.58 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.68 (t, *J* = 7.8 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 5.46 (s, 2 H, CH_2NNN), 7.19 (s, 1 H, CH), 7.27 (m, 5 H, Ph). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.7 ($CH_2CH_2CH_2CH_3$), 22.1 ($CH_2CH_2CH_2CH_3$), 25.3 ($CH_2CH_2CH_2CH_3$), 31.3 ($CH_2CH_2CH_2CH_3$), 53.8 ($PhCH_2$), 120.5 ($CH_{triazole}$), 127.8 (CH_o), 128.4 (CH_m), 128.9 (CH_p), 134.8 (C_{Ph}), 148.8 ($C_{triazole}$).
Compound 3e: $[\alpha]_D^{25}$ –80.3 (*c* 0.02, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.96 (m, 4 H, $NCbzCHCH_2CH_2$), 3.48 (m, 2 H, $NCbzCH_2$), 4.30 (m, 1 H, NCbzCH), 5.00 (m, 2 H, $PhCH_2NNN$), 5.17 (m, 2 H, $COOCH_2$), 5.34 (s, 1 H, $NCOOCH_2Ph$), 5.42 (s, 1 H, $NCOOCH_2Ph$), 7.23 (m, 10 H, 2 × Ph), 7.56 (s, 1 H, $CH_{triazole}$). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.5 ($NCbzCH_2CH_2$), 30.0 ($NCbzCHCH_2$), 46.4 ($NCbzCH_2$), 53.7 ($PhCH_2NNN$), 57.9 ($COOCH_2$), 58.7 (NCbzCH), 66.5 ($PhCH_2OCON$), 123.3 ($CH_{triazole}$), 127.2–128.7 (CH_{Ph}), 134.2 ($NNNCH_2C$), 136.3 ($NCOOCH_2C$), 142.6 ($CHCOOCH_2C$), 154.2 ($NCOOCH_2Ph$), 172.2 ($CHCOOCH_2$).
Compound 3g: $[\alpha]_D^{25}$ –260.7 (*c* 0.033, $CHCl_3$). H NMR (300.13 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.5 Hz, 3 H, $CH_2CH_2CH_2CH_2CH_3$), 1.27 (m, 5 H, $CH_2CH_2CH_2CH_2CH_3$ + NCbzCHCHH), 1.61 (m, 3 H, NCbzCHCHHCH$_2$), 1.89 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 2.60 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 3.15 (m, 1 H, NCbzCHH), 3.33 (m, 1 H, NCbzCHH), 4.10 (m, 1 H, NCbzCH), 4.48 (m, 2 H, $CHCH_2NNN$), 5.13 (m, 2 H, $PhCH_2$), 6.88 (s, 0.7 H, $CH_{triazole}$), 7.10 (s, 0.3 H, $CH_{triazole}$), 7.31 (m, 5 H, Ph). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.8 ($CH_2CH_2CH_2CH_2CH_3$), 22.2 ($CH_2CH_2CH_2CH_2CH_3$), 23.1 (NCbzCHCHH), 25.3 ($CH_2CH_2CH_2CH_2CH_3$), 27.8 ($CH_2CH_2CH_2CH_2CH_3$), 28.9 ($NCbzCHCH_2CH_2$), 31.1 ($CH_2CH_2CH_2CH_2CH_3$), 46.8 ($NCbzCH_2$), 51.5 (CH_2NNN), 57.1 ($CHCH_2NNN$), 66.9 ($PhCH_2$), 121.2 ($CH_{triazole}$), 127.7–128.4 (CH_{Ph}), 136.3 (C_{Ph}), 148.3 ($C_{triazole}$), 154.5 (NCOO).
Compound 5a: ^{1}H NMR (400.13 MHz, CD_3CN): δ = 0.92 (t, *J* = 7.6 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 1.40 (sext, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 1.65 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.81 (t, *J* = 7.2 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 4.12 (s, 3 H, N^+Me), 5.82 (s, 2 H, CH_2NNN), 7.46 (m, 5 H, Ph), 8.70 (s, 1 H, CH). Signals at δ = 2.81 and 4.12 ppm showed a weak cross peak with each other in the NOESY spectrum. ^{13}C NMR (100.61 MHz, CD_3CN): δ = 13.5 ($CH_2CH_2CH_2CH_3$), 22.2 ($CH_2CH_2CH_2CH_3$), 23.4 ($CH_2CH_2CH_2CH_3$), 29.0 ($CH_2CH_2CH_2CH_3$), 38.5 (N^+Me), 57.1 ($PhCH_2$), 117.9 ($CH_{triazole}$), 128.8 (CH_o), 129.6 (CH_m), 130.0 (CH_p), 133.0 (C_{Ph}), 145.5 ($C_{triazole}$).
Compound 5e: $[\alpha]_D^{25}$ –36.1 (*c* 0.024, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.87 (m, 4 H, $NCbzCHCH_2CH_2$), 3.40 (m, 2 H, $NCbzCH_2$), 4.06 (s, 3 H, N^+Me), 4.21 (m, 1 H, NCbzCH), 4.89 (m, 2 H, $PhCH_2NNN$), 5.45 (m, 2 H, $COOCH_2$), 5.34 (s, 1 H, $NCOOCH_2Ph$), 5.42 (s, 1 H, $NCOOCH_2Ph$), 7.27 (m, 10 H, 2 × Ph), 8.87 (s, 1 H, $CH_{triazole}$). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.1 ($NCbzCH_2CH_2$), 29.9 ($NCbzCHCH_2$), 39.3 (N^+Me), 46.3 ($NCbzCH_2$), 54.2 ($PhCH_2NNN$), 57.0 ($COOCH_2$), 58.6 (NCbzCH), 66.5 ($PhCH_2OCON$), 123.3 ($CH_{triazole}$), 127.0–130.6 (CH_{Ph}), 135.9 ($NNNCH_2C$), 138.3 ($NCOOCH_2C$), 142.3 ($CHCOOCH_2C$), 153.9 ($NCOOCH_2Ph$), 171.5 ($CHCOOCH_2$).
Compound 5g: $[\alpha]_D^{25}$ –72.9 (*c* 0.02, $CHCl_3$). ^{1}H NMR (300.13 MHz, CD_3CN): δ = 0.87 (t, *J* = 6.5 Hz, 3 H, $CH_2CH_2CH_2CH_2CH_3$), 1.31 (m, 5 H, $CH_2CH_2CH_2CH_2CH_3$ + NCbzCHCHH), 1.58 (m, 3 H, NCbzCHCHHCH$_2$), 1.87 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 2.39 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 3.16 (m, 1 H, NCbzCHH), 3.34 (m, 1 H, NCbzCHH), 3.90 (m, 1 H, NCbzCH), 4.07 (s, 3 H, N^+Me), 4.51 (m, 2 H, $CHCH_2NNN$), 5.12 (m, 2 H, $PhCH_2$), 7.35 (m, 5 H, Ph), 8.55 (s, 1 H, $CH_{triazole}$). ^{13}C NMR (75.47 MHz, CD_3CN): δ = 14.0 ($CH_2CH_2CH_2CH_2CH_3$), 22.6 ($CH_2CH_2CH_2CH_2CH_3$), 23.5 (NCbzCHCHH), 25.7 ($CH_2CH_2CH_2CH_2CH_3$), 27.1 ($CH_2CH_2CH_2CH_2CH_3$), 28.6 ($NCbzCHCH_2CH_2$), 31.2 ($CH_2CH_2CH_2CH_2CH_3$), 38.3 (N^+Me), 47.3 ($NCbzCH_2$), 51.6 (CH_2NNN), 57.6 ($CHCH_2NNN$), 67.0 ($PhCH_2$), 118.1 ($CH_{triazole}$), 128.1–129.7 (CH_{Ph}), 137.8 (C_{Ph}), 146.8 ($C_{triazole}$), 155.6 (NCOO).
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