

Preparation of Propargyl Amines in a ZnCl₂-Dimethylurea Deep-Eutectic Solvent

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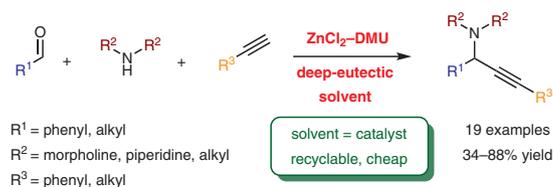
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Abstract The coupling of an aldehyde, an amine, and an alkyne to yield propargyl amines was performed in a deep-eutectic solvent composed of zinc chloride and dimethylurea. The deep-eutectic solvent acts simultaneously as catalyst and solvent giving access to a variety of propargyl amines, which were isolated in moderate to very good yields.

Key words deep-eutectic solvent, zinc chloride, dimethylurea, A³-coupling, propargyl amine

Deep-eutectic solvents (DES) have been continuously investigated in academic and applied research for more than a decade. DES are nontoxic, biodegradable, cheap, easy to prepare, possess a low vapour pressure and often good thermal stability.^{1–3} A first report on DES dates back to 2003, when Abbott et al. described the formation of DES based on quaternary ammonium salts and urea.⁴ In general, a DES is defined as a mixture of two or three components forming an eutectic with a lower melting point than each of the pure components. Due to the formation of hydrogen bonds and other noncovalent interactions, the melting point of a typical DES is below 100 °C; some DES are liquid even at room temperature.¹ Most DES consist of a hydrogen bond donor and a hydrogen bond acceptor. In this context, hydrogen bond donors can be alcohols, saccharides, carboxylic acids, and urea derivatives. Hydrogen bond acceptors can be organic halide salts, such as ammonium salts (choline chloride, for example). Metal salts, such as ZnCl₂, FeCl₃, and SnCl₂, can also form a DES with a hydrogen bond donor.⁵ DES have received substantial interest as solvents for organic syntheses, for example in metal-catalyzed transformations like the azide-alkyne cycloaddition and palladium-catalyzed C–C coupling reactions, which were performed in saccharide-based DES.^{6,7} Furthermore, organolithium and

Grignard reagents were reacted with ketones and imines in choline chloride–glycerol DES.^{8,9} An elegant approach is the application of a DES acting as solvent and catalyst simultaneously. For example, DES based on tartaric acid and urea derivatives were used in the synthesis of indoles,¹⁰ pyrimidopyrimidinediones,¹¹ dihydropyrimidinones,¹² and hydantoin.¹³

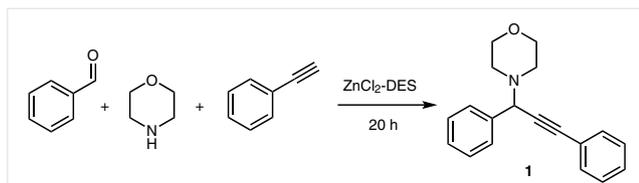
The A³-coupling is a three-component reaction of an amine, an aldehyde, and an alkyne, leading to a propargyl amine. It is catalyzed by transition-metal ions, such as Cu(I), Cu(II), Zn(II), and Fe(III). The amine and the aldehyde react to form an iminium ion *in situ*, followed by attack of the metal-activated alkyne. Due to the facile availability of propargyl amines, the A³-coupling is a valuable tool for the synthesis of N-heterocycles.¹⁴ During the last decade, the A³-coupling has been investigated extensively and various approaches were developed, exploring the scope of the starting materials, choice of metal catalysts and reaction medium. For example, the reaction was performed under solvent-free conditions,¹⁵ in ionic liquids,¹⁶ and catalyzed by magnetic nanoparticles in a DES.¹⁷

Several DES with a metal salt as one of the components are reported and some were already applied in synthesis. In particular, a DES formed by zinc chloride and choline chloride was used as solvent and catalyst, for example, in the synthesis of amides from aldehydes and nitriles,¹⁸ alkylation¹⁹ and acylation²⁰ of arenes, and acylation of alcohols.²¹

The fact that zinc salts are effective catalysts for the A³-coupling^{22,23} motivated us to perform the A³-coupling in a DES based on a zinc salt. In this system, the zinc salt would act as one of the DES components and catalyst simultaneously, making the addition of an external metal catalyst unnecessary due to the dual role of the reaction medium.

As zinc chloride is reported to form DES with several hydrogen bond donors,^{1,5} we chose this salt as one of the DES components. Choline chloride, acetamide, urea, and di-

methylurea were tested as second DES component, and the coupling of benzaldehyde, morpholine, and phenylacetylene, leading to propargyl amine derivative **1**, was chosen to optimize the reaction conditions (Scheme 1, Table 1).



Scheme 1 Reaction of benzaldehyde, morpholine, and phenylacetylene, leading to propargyl amine derivative **1**

Table 1 Screening of hydrogen bond donors for the synthesis of propargyl amine derivative **1**

Entry	H bond donor	Ratio ZnCl ₂ /H bond donor	Temp (°C)	Yield (%)
1	choline chloride	2:1	100	traces
2	acetamide	1:4	80	33
3	acetamide	1:4	100	traces
4	urea	2:7	80	phase separation
5	dimethylurea	2:7	80	67

The DES were simply prepared by mixing the two solid components and heating the mixture until a clear liquid occurred. First, ZnCl₂-choline chloride (2:1) was tested at 100 °C. Only traces of the product were formed (Table 1, entry 1). Drawbacks of this approach are the high viscosity of the DES, which necessitated high reaction temperature due to its high melting point and its high hydrophilicity: The starting materials were not completely soluble in the DES, forming a turbid emulsion. To overcome these problems, ZnCl₂-acetamide (1:4) was investigated, possessing lower viscosity and higher hydrophobicity. The starting materials were soluble in the DES, and the product was isolated in 33% yield (Table 1, entry 2). At higher temperature (100 °C) only traces of product were isolated (Table 1, entry 3). Therefore, the system was not investigated further. In ZnCl₂-urea (2:7), the starting materials did not dissolve, forming a separate layer (Table 1, entry 4). Hence, the more hydrophobic ZnCl₂-dimethylurea (2:7) was tested. Fortunately, the starting materials dissolved readily in this DES, forming a homogeneous reaction mixture, and the product was isolated in 67% yield (Table 1, entry 5).

With this encouraging observation, the optimization was continued with ZnCl₂-dimethylurea (Table 2). First, the reaction temperature was varied, applying one equivalent of morpholine and one equivalent of phenylacetylene for 20 hours. Decreased reaction temperature (60 °C) resulted in lower yield (52%, Table 2, entry 1), similar to a higher reac-

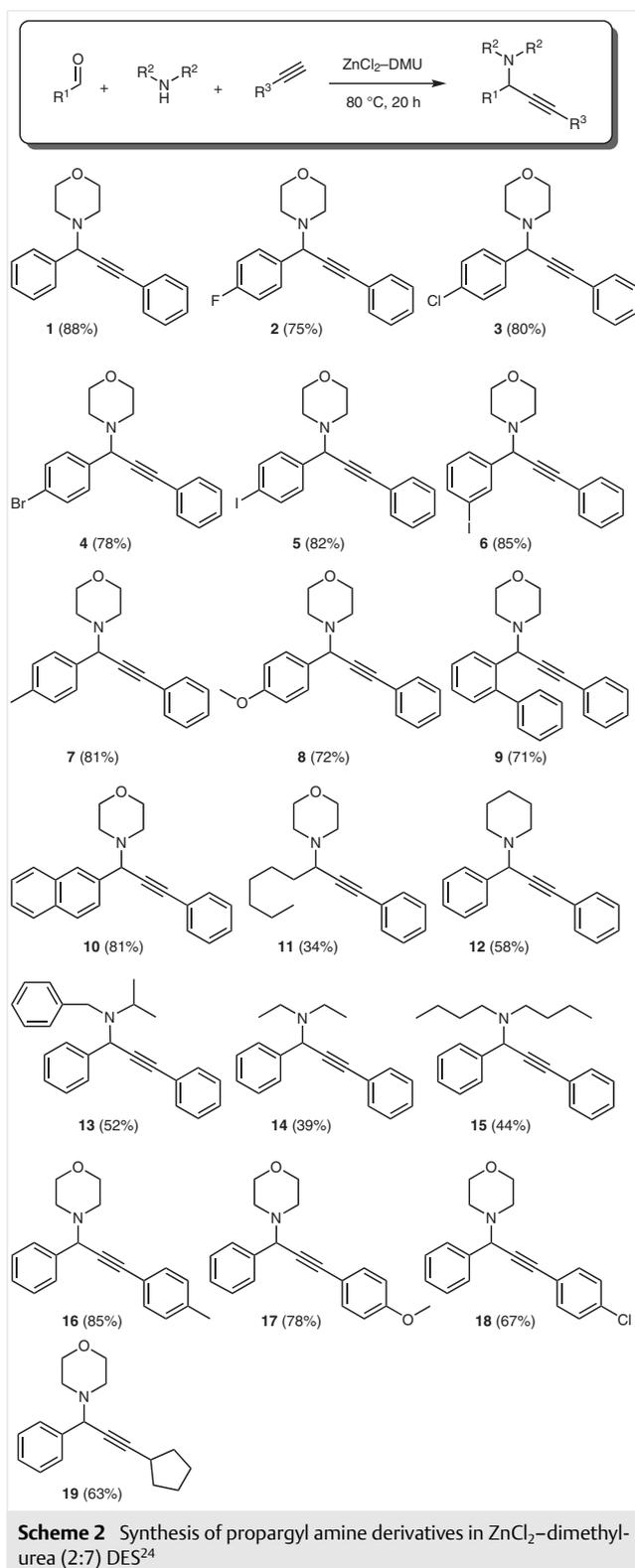
tion temperature of 100 °C, which decreased the yield to 59% (Table 2, entry 3).

Table 2 Optimization of reaction conditions for the synthesis of propargyl amine derivative **1** in ZnCl₂-dimethylurea (2:7)

Entry	Temp (°C)	Morpholine (equiv)	Phenylacetylene (equiv)	Yield (%)
1	60	1	1	52
2	80	1	1	67
3	100	1	1	59
4	80	1.1	1.2	73
5	80	1.2	1.3	77
6	80	1.5	1.5	88

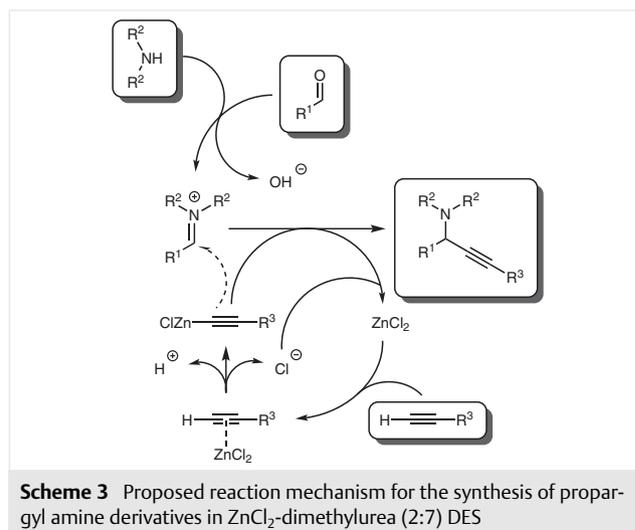
Next, higher amounts of morpholine and phenylacetylene were applied. A slight excess of morpholine (1.1 equiv) and phenylacetylene (1.2 equiv) relative to benzaldehyde increased the yield to 73% (Table 2, entry 4); similarly, a small increase in yield could be achieved by applying 1.2 equivalents of morpholine and 1.3 equivalents of phenylacetylene (77%, Table 2, entry 5). When 1.5 equivalents of morpholine and 1.5 equivalents of phenylacetylene were applied, the product was isolated in very good yield (88%, Table 2, entry 6). To summarize, under optimized conditions using 1.5 equivalents of amine and 1.5 equivalents of alkyne in ZnCl₂-dimethylurea (2:7), DES at 80 °C gave the best results.

Having optimized the reaction conditions, the scope of the aldehyde, amine, and alkyne component was investigated, starting with variation of the aldehyde component and reaction with morpholine and phenylacetylene (Scheme 2). The application of benzaldehyde derivatives with halogen atoms in *para* position resulted in the products **2–5** with good to very good yields. Similarly, 3-iodobenzaldehyde furnished the corresponding propargyl amine derivative **6** in very good yield. The reaction of 4-methylbenzaldehyde resulted in 81% yield of product **7**, whereas the presence of a methoxy group in *para* position lowered the yield to 72% (product **8**), which is probably due to the decrease in electrophilic character of the carbonyl group. A similar yield was achieved with a phenyl group in *ortho* position (product **9**). 2-Naphthaldehyde as aldehyde component resulted in 81% of product **10**, while aliphatic heptanal gave product **11** in a low isolated yield of 34%. Next, the amine component was varied. In all cases, the product yields were significantly lower than for morpholine. While the use of piperidine and isopropylbenzylamine resulted in moderate yields (58%, product **12**; 52%, product **13**), the linear aliphatic amines diethylamine and dibutylamine gave about 40 % (products **14** and **15**). Finally, the effect of substitution on the alkyne component was studied, by varying the *para*



substitution on phenylacetylene. 4-Methylphenylacetylene resulted in 85% of product **16**. 4-Methoxy- and 4-chloro substitution decreases the yield slightly (products **17** and **18**). Aliphatic cyclopentylacetylene resulted in good yield of product **19** (63%).

A plausible reaction mechanism for the synthesis of propargyl amine derivatives is shown in Scheme 3. ZnCl_2 coordinates to the alkyne and forms an acetylide, which attacks the iminium ion generated from the aldehyde and the amine. Upon formation of the propargyl amine, ZnCl_2 is released.



Finally, the recyclability of the ZnCl_2 -dimethylurea DES was tested, and product **1** could be isolated in very good yield applying the same DES for three cycles (see the Supporting Information).

In summary, a ZnCl_2 -dimethylurea DES is an interesting alternative reaction medium for the synthesis of propargyl amine derivatives. The recyclable DES acts simultaneously as catalyst and solvent and is prepared from cheap chemicals.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1588571>.

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- (24) **General Procedure for the Synthesis of Propargyl Amines**
The aldehyde was added to the DES (for preparation of DES, see the Supporting Information), followed by the amine (1.5 equiv) and the alkyne (1.5 equiv), and the reaction was performed at 80 °C for 20 h. For workup, the hot reaction mixture was diluted with 2 mL water and extracted four times with 5 mL EtOAc. The combined organic layers were dried over Na₂SO₄, and the product was isolated applying flash column chromatography (gradient of EtOAc in PE).
4-[1-(4-Iodophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (5)
4-Iodobenzaldehyde (232 mg, 1.0 mmol) was reacted with morpholine (131 µL, 1.5 mmol) and phenylacetylene (165 µL, 1.5 mmol). The reaction was performed in 1 g of melt, prepared from 0.31 g ZnCl₂ and 0.69 g DMU; yield 336 mg (82%). ¹H NMR (300 MHz, CDCl₃): δ = 7.73–7.69 (m, 2 H), 7.57–7.51 (m, 2 H), 7.43–7.40 (m, 2 H), 7.37–7.32 (m, 3 H), 4.74 (s, 1 H), 3.80–3.68 (m, 4 H), 2.63 (t, J = 4.5 Hz, 4 H). ¹³C NMR (75 MHz, CDCl₃): δ = 137.8, 137.4, 131.9, 130.6, 128.5, 128.4, 122.7, 93.6, 89.0, 84.3, 67.1, 61.4, 49.9. ESI-MS: m/z calcd for C₁₉H₁₈INO [MH]⁺: 404.0512; found: 404.0533. EA (%), theoretical values in brackets): C, 56.50 (56.59); H, 4.36 (4.50); N, 3.38 (3.47).