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Straightforward synthesis of alkynyl imines via 1,2-elimination of α,α-dichloroketimines

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Abstract—Alkylation of α,α-dichloroketimines at the α-position with benzyl bromides afforded β-arylated α,α-dichloroketimines in good yields. The latter imines could be easily transformed to the corresponding alkynyl imines, a synthetically important class of compounds, via 1,2-elimination of HCl upon treatment with 2 equiv of sodium hydride in DMSO or potassium *tert*-butoxide in THF.

Alkynyl imines represent an important class of functionalized alkynes because of their applications in the synthesis of a broad range of biologically important compounds. Reduction of the imino function provides access to propargyl amines, which are active as monoamine oxidase inhibitors.[1] *N*-Methylation to iminium salts gives rise to reactive dienophiles for Diels–Alder reactions.[2] Cyclization reactions of alkynyl imines have been used for the synthesis of pyrrolinones,[3] pyrroles,[4] 2-pyridones,[5] pyrazoles and pyrimidines,[6] quinolines and fused pyrrolines.[7] Cyclization of the corresponding alkynyl hydrazones has led to the synthesis of different pyrazoles.[8] Despite their synthetic importance, relatively few methods to synthesize alkynyl imines have been described. One important methodology involves metal-catalyzed coupling reactions of imidoyl halides,[2,6,9] or *C*,*N*-diarylnitrones,[10] or the palladium-catalyzed reaction product of bromobenzene and *tert*-butyl isocyanide,[11] with organometallic reagents derived from 1-alkynes. Alternatively, alkynyl imines have been prepared via imination of the corresponding alkynyl ketones.[4,8d,12] An interesting report has also been made on the condensation reaction of α-chloroacetophenone *O*-methyloxime derivatives to furnish alkynyl oxime ethers via a [2+2]-cycloreversion of an azacyclobutadiene intermediate.[13] Surprisingly, elimination reactions toward alkynyl imines have hardly been described. Reaction of dianions of 1-arylenaminones with trimethylchlorosilane leads to alkynyl imines in moderate yield via an unexpected elimination.[14] In the present report, an efficient and straightforward synthesis of benzimidoyl-substituted alkynes is described based on two 1,2-eliminations of HCl from β-arylated α,α-dichloroketimines formed via alkylation of imines derived from α,α-dichloroacetophenone derivatives.

Based on the reported formation of *N*-[1-(4-chlorophenyl)-3-phenyl-2-propyn-1-ylidene]ethylamine **3** via elimination of α-chloro-β-mesyloxy imine **4** as a side-reaction during the cyclization of *N*-ethyl-β-mesyloxyamine **1** to the corresponding 3,3-dichloroazetidine **2** (Scheme 1),[15] it was envisaged that β-arylated imines with two leaving groups in α-position are potential substrates for the synthesis of benzimidoyl-substituted alkynes.

α,α-Dichloroketimines **5**[16] were deprotonated with lithium diisopropylamide (LDA) in tetrahydrofuran at 0 °C to give the corresponding 3,3-dichloro-1-azaallylic anions, which reacted with benzyl bromides at −78 °C. After further reaction at room temperature for 24 h, the β-arylated α,α-dichloro imines **6** could be isolated (56–94% yield) as pure crystalline compounds after recrystallization from methanol (Scheme 2, Table 1).[17] All compounds **6** occurred exclusively as the *E*-isomer.

The reactivity of the β-arylated α,α-dichloro imines **6** was studied with different bases in different solvents.

Keywords: Alkynyl imines; 3,3-Dichloro-1-azaallylic anions; 1,2-Elimination; Alkynyl ketones.
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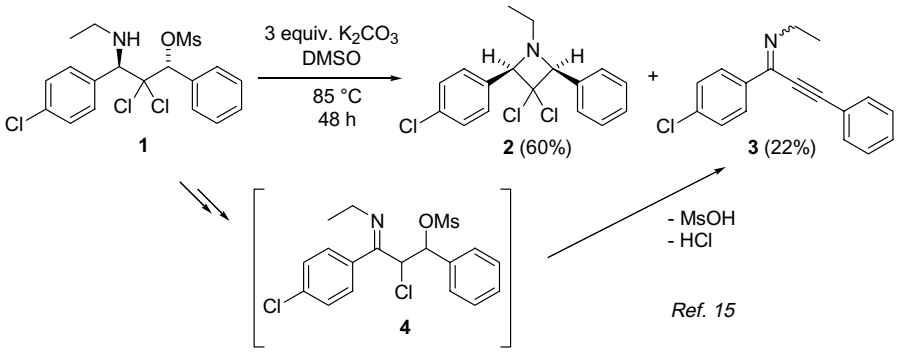
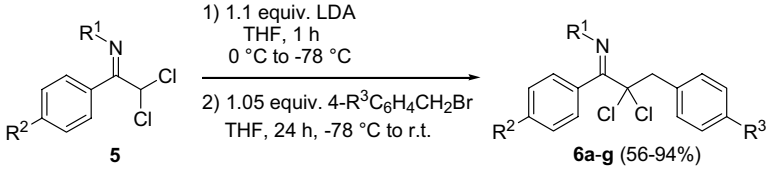


Scheme 1.



Scheme 2.

Table 1. Synthesis of β-arylated α,α-dichloro imines **6** from α,α-dichloro imines **5**

Imine **6**	R^1	R^2	R^3	Yield[a] (%)
6a	*i*Pr	H	Cl	86
6b	*i*Pr	Cl	H	94
6c	*i*Pr	H	MeO	74
6d	*i*Pr	H	Me	76
6e	*i*Pr	Me	H	72
6f	*i*Pr	H	H	86
6g	*c*Hex	H	H	56

[a] Isolated yields after recrystallization from methanol.

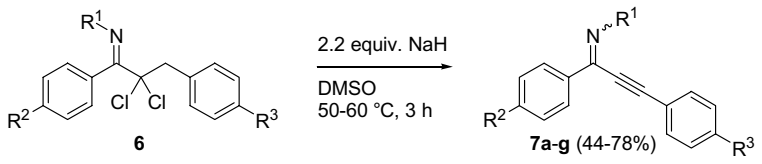
No reaction was observed upon the treatment of imine **6a** with sodium hydride in tetrahydrofuran at 50–60 °C for several hours or upon the reaction of imine **6f** with $LiCl/Li_2CO_3$ in dimethylformamide at 70 °C for 4 h,[18] or upon refluxing imine **6f** in pyridine for 3 h. In contrast, the use of 2.2 equiv of dimsylsodium in dimethyl sulfoxide afforded the desired alkynes **7**, as single isomers, via two consecutive 1,2-eliminations of HCl in moderate to good yields after purification by column chromatography (Scheme 3, Table 2).[19] The yield of alkynes **7a** and **7e** could be improved by reacting α,α-dichloroketimines **6a** and **6e** with 2.2 equiv of potassium *tert*-butoxide in tetrahydrofuran at 50–60 °C for 3 h (Table 2). Upon reaction with sodium methoxide, 2 N in methanol, at 55 °C for 3 h only complex reaction mixtures were isolated.

Hydrolysis of alkynyl imines to the corresponding alkynyl ketones has been described via aqueous acid hydrolysis with oxalic acid[20] or hydrochloric acid.[1a] However, hydrolysis of imine **7f** with 2 N oxalic acid in aqueous diethyl ether afforded an intractable mixture of compounds. Treatment of imines **7a** and **7f** with 2 N hydrochloric acid in aqueous tetrahydrofuran resulted in the formation of β-chloro-α,β-unsaturated ketones **8a**,**f**,[21] representatives of the synthetically useful class of β-chlorovinyl ketones,[22] due to the addition of hydrogen chloride to alkynyl ketones **9**. The latter reaction is analogous to the known reaction of alkynyl ketones with hydrogen chloride.[23] In contrast, alkynyl ketones

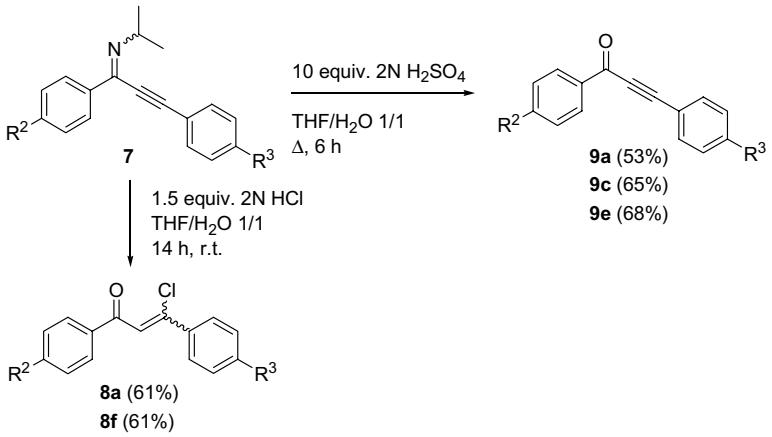
Table 2. Synthesis of alkynes **7** from dehydrochlorination of β-arylated α,α-dichloro imines **6** with dimsylsodium in dimethyl sulfoxide

Alkyne **7**	R^1	R^2	R^3	Yield[a] (%)
7a	*i*Pr	H	Cl	44 (85)[b]
7b	*i*Pr	Cl	H	62
7c	*i*Pr	H	MeO	73
7d	*i*Pr	H	Me	56
7e	*i*Pr	Me	H	68 (79)[b]
7f	*i*Pr	H	H	78
7g	*c*Hex	H	H	76

[a] Isolated yields after column chromatography.
[b] Isolated yields after column chromatography from reaction with 2.2 equiv potassium *tert*-butoxide in tetrahydrofuran.



Scheme 3.



Scheme 4.

9a,**c**,**e** were obtained as pure crystalline compounds upon hydrolysis with 2 N sulfuric acid in aqueous tetrahydrofuran (Scheme 4).[24]

In conclusion, a short and efficient synthesis of diaryl-substituted alkynyl imines, a class of versatile intermediates in the synthesis of nitrogen-containing compounds, has been achieved based on an unreported double 1,2-elimination strategy of β-aryl-α,α-dichloro imines formed via alkylation of *N*-isopropyl- or *N*-cyclohexyl-3,3-dichloro-1-azaallylic anions. This alkylation and elimination strategy should be applicable toward the synthesis of other N-substituted alkynyl imines as well.

Acknowledgments

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17. *General procedure*: To an ice-cooled solution of diisopropylamine (0.97 g, 9.6 mmol) in dry THF (9 mL) was added under a N_2 atmosphere *n*-BuLi (3.8 mL, 2.5 M in hexane, 9.6 mmol) followed after 10 min by a solution of α,α-dichloro imine **5** (8.7 mmol) in THF (9 mL). The reaction was cooled over a period of 1 h to −78 °C and then a solution of benzyl bromide (9.1 mmol) in THF (9 mL) was added dropwise. The mixture was stirred for 1 h at −78 °C and gradually warmed to room temperature for 24 h. The reaction mixture was poured into aq. NaOH (0.5 N, 30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried ($MgSO_4$/K_2CO_3), filtered and evaporated. The crude reaction mixture was purified by recrystallization (MeOH) to afford the pure crystalline imine **6** (56–94% yield). *N*-(2,2-dichloro-1,3-diphenylpropylidene)propyl-2-amine **6f**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.11$ (d, 6H, $J = 6.05$ Hz, $(CH_3)_2$), 3.27 (septet, 1H, $J = 6.2$ Hz, $CH(CH_3)_2$), 3.98 (s, 2H, CH_2), 7.14–7.50 (m, 10H, 10 × CH_{ar}); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 23.3$, 49.7, 53.5, 90.8, 127.2, 127.6, 127.8, 128.5, 128.6, 132.2, 134.2, 135.5, 165.0; IR (KBr, cm^{-1}): $\nu = 1645$; MS (ES,

pos. mode): *m*/*z* (%): 320/22/24 ($M+H^+$, 100). Yield = 86%. Mp = 110.0–110.3 °C. White crystals.

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19. *General procedure*: To sodium hydride (0.15 g, 6.2 mmol) was added DMSO (6 mL) and the mixture was stirred for 20 min at room temperature to generate dimsylsodium. Subsequently, α,α-dichloro imine **6** (2.82 mmol), dissolved in DMSO (9 mL), was added dropwise at room temperature. After completion of the addition, the mixture was kept at 55 °C for 3 h. After cooling, water (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine (3 × 15 mL), dried ($MgSO_4$) and after filtration and evaporation of the solvent, the crude alkynyl imine **7** was obtained. Further purification was performed by column chromatography on silica gel (petroleum ether/EtOAc 99:1) to yield the pure compound **7** (44–78% yield). *N*-(1,3-Diphenylprop-2-yn-1-ylidene)-2-methylethylamine **7f**. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.32$ (d, 6H, $J = 6.33$ Hz, $(CH_3)_2$), 4.33 (septet, 1H, $J = 6.33$ Hz, $CH(CH_3)_2$), 7.37–7.44 (m, 6H, 6 × CH_{ar}), 7.56–7.61 (m, 2H, 2 × CH_{ar}), 8.04–8.09 (m, 2H, 2 × CH_{ar}); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 23.5$, 56.3, 81.5, 97.5, 121.7, 127.5, 128.2, 128.6, 129.5, 130.2, 132.1, 137.9, 148.3; IR (NaCl, cm^{-1}): $\nu = 2204$, 1591; MS (ES, pos. mode): *m*/*z* (%): 248 ($M+H^+$, 100). Yield = 78%. $R_f = 0.35$ (petroleum ether/EtOAc 9:1). Colorless viscous oil.
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24. *General procedure*: To a solution of alkynyl imine **7** (0.72 mmol) in THF (3.6 mL) was added aq. H_2SO_4 (2 N, 3.6 mL, 7.2 mmol). The reaction mixture was stirred for 6 h under reflux. The reaction mixture was poured into aq NaOH (0.5 N, 20 mL) and extracted with Et_2O (30 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated. The crude reaction mixture was purified by recrystallization (MeOH) to afford the pure crystalline alkynyl ketone **9** (53–68% yield). The spectral data of ketones **9** were in full agreement with reported data.[8d]