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Title: Superbase-Catalyzed Synthesis of Propargylamines from Ketimines and Acetylenes

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Transition-Metal-Free Addition of Acetylenes to Ketimines: the First Base-Catalyzed Ethynylation of the C=N Bond

Ivan A. Bidusenko, Elena Yu. Schmidt, Igor A. Ushakov, and Boris A. Trofimov*

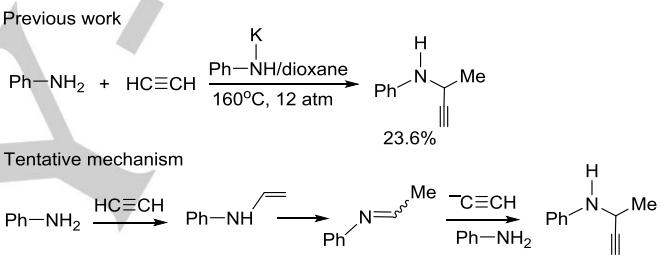
Abstract: A one-pot transition metal-free synthesis of propargylamines in good to excellent yield from ketone-derived imines and aryl- and hetarylacetylenes in the presence of KOBu^t/DMSO superbase system (40^{o}C, 10 min) has been developed. The reaction involves a nucleophilic addition of acetylenic carbanions to the C=N bond thus for the first time featuring the aza-Favorsky reaction.

Currently, propargylamines are increasingly becoming the privileged molecules owing to their synthetic[1] and pharmaceutical[2] importance. Since the pioneering syntheses of these compounds by aminoalkylation of acetylenes published by Mannich[3] and Reppe,[4] the research in this field was not too intensive until 2001, when iridium-catalyzed three-component reaction between primary amines, aldehydes and acetylenes to give propargylamines was reported.[5] Afterwards, the research activity on this synthesis, which is now abbreviated as A^3 condensation, has acquired an avalanche-like character.[1,6] Originally performed as the catalyst-free[3] or copper-catalyzed[4] process, now it is carried out in the presence of various transition metal catalysts.[1c] Still, newer catalytic systems and protocols keep being claimed.[7] However, such three-component reactions involving ketones (especially aromatic ketones), amines and alkynes (KA^2 coupling) are far from being developed enough because of a lower reactivity observed for ketones in this process .[8, 9, 10]

Since it has been shown[7g, 8] that the preformed aldimines react with acetylenes slower to give propargylamines in poorer yields, a most probable key step of A^3 condensation is the nucleophilic substitution of the hydroxyl group in intermediate α-hydroxyalkylamines by π/σ-metal acetylene complexes. The known limitation of A^3 condensation is that it meets certain difficulties when extended over the ketones, sometimes requiring additional microvawe activation[9] or special transition-metal-based catalytic systems.[10]

This work presents a successful attempt to overcome this limitation by the development of superbase-catalyzed ethynylation of ketone-derived imines, i.e. to extend the Favorsky alkynylation of ketones[11] over their nitrogen analogues (ketimines). Actually, from point of view of the basic chemistry, the C=N bond, like C=O bond, can accept the nucleophilic attack by acetylenic anions to give propargylamines (congeners of Favorsky propargylalcohols). Because of a lower electrophilicity of the C=N bond compared to that of the C=O bond, the acetylenic anions should be in a higher concentration and of a stronger nucleophilicity to accomplish the target addition.

Indeed, earlier it was published a one-pot synthesis of 3-arylamino-1-butynes in 25-30% yields from aniline[12] or N-arylamides[12b,13] and acetylene in the superbase media like potassium phenylamide/dioxane or potassium acetyl(aryl)amide/THF. The reaction was assumed to proceed via nucleophilic addition of acetylenic anion to the intermediate arylimine (the initial product of aniline vinylation, Scheme 1).[12,13]



Scheme 1. Superbase-catalyzed one-pot synthesis of 3-arylamino-1-butyne from aniline and acetylene.[12]

We have started the present study with the question whether the base-catalyzed ethynylation of ketimines is possible and, if yes, which base catalyst is most suitable for further development of this reaction. We have chosen the interaction of ketimine **1a** (acetophenone/aniline Schiff adduct) with phenylacetylene **2a** as a reference reaction and as probable catalytic systems were taken combination of alkali metal hydroxides or alkoxides with different solvents, which can significantly change the total basicity of the system, sometimes producing superbases like KOBu^t/DMSO (pKa 30-32).[14]

The selected experimental results (Table 1) show that the base-catalyzed ethynylation of the C=N bond is indeed possible. Expectedly, the best catalytic systems proved to be superbasic pairs KOBu^t/DMSO and KOBu^t/DMF securing 46 and 48% yields of the target propargylamine **3a** at 20^{o}C for 2 h (entries 5,6), whereas other base/solvent combinations were inactive. When the reactants (ketimine **1a** + acetylene **2a**) were allowed to contact without a base (entry 1), no reaction was observed.

Indeed, according to the literature data,[8, 9, 10] KA^2 condensations are catalyzed by transition metals used in amounts of not less than 5 mol%, usually 20 mol%. Therefore, if even trace amounts of transition metals are present in the reaction mixture, they cannot catalyze these processes.

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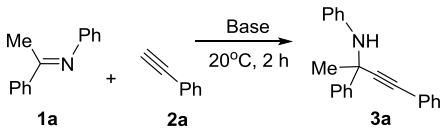
Table 1. Effect of base/solvent combination on the reaction of ketimine **1a** with acetylene **2a**.[a]



1a **2a** **3a**

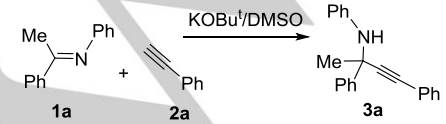
Entry	Base	Solvent	Yield (%)[b]
1	_	DMSO	0
2	NaOH	DMSO	traces
3	KOH	DMSO	28
4	NaOBu^t	DMSO	37
5	KOBu^t	DMSO	48 (45)[c]
6	KOBu^t	DMF	46 (41)[c]
7	KOBu^t	NMP	n.d.
8	KOBu^t	THF	traces
9	KOBu^t	1,4-dioxane	n.d.
10	KOBu^t	toluene	n.d.

[a] Reaction conditions: **1a** (1 mmol, 195 mg), **2a** (1 mmol, 102 mg), base (1 mmol), solvent (3 mL), 20°C, 2 h; [b] According to ^{1}H NMR data of the crude product ($CDCl_3$, *n*-dodecane was used as an internal standard); [c] Isolated yield after column chromatography (SiO_2, *n*-hexane/ethyl acetate, 50:1). n.d. = not detected.

Next, using the KOBu^t/DMSO superbase catalyst we have examined the influence of its concentration, the reactants ratio, reaction temperature and time on the process efficiency aiming to improve it (to increase yield of the target product **3a** and to shorten the reaction time).

As seen from the selected results (Table 2), the yield of propargylamine **3a** can reach 70%, when the reactants were allowed to contact at 40°C during just 10 min. The further increase of the reaction time 10 → 30 →120 min did not lead to a higher yield. On the contrary, it slightly dropped from 70 → 68 → 64%, thus implying a slow transformation of the propargylamine formed. Indeed, when pure propargylamine **3a** was kept for 120 min at 40°C in the same system after the workup of the reaction mixture, 5% loss of the propargylamine was observed. Probably, in this case, a slow superbase-catalyzed head-to-tail polycondensation of the final product and/or anionic polymerization across the acetylenic moiety occur.

Table 2. Effects of the reactant/KOBu^t ratio, temperature and time on the yield of **3a**.[a]



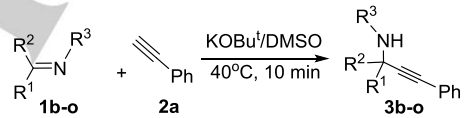
1a **2a** **3a**

Entry	**1a**:**2a**:KOBu^t[b]	*T* (°C)	t (min)	Yield (%)[c]
1	1:1:1	15	120	36
2	1:1:1	20	120	45
3	1:1:1	40	120	59
4	1:1:1	50	120	56
5	1:1:1	60	120	49
6	1:1.5:1	40	120	62
7	1:1.5:0.5	40	5	63
8	1:1.5:0.5	40	10	70
9	1:1.5:0.5	40	30	68
10	1:1.5:0.5	40	120	64
11	1:1.5:0.2	40	120	28

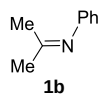
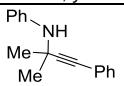
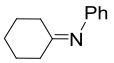
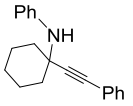
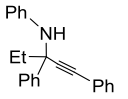
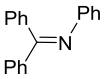
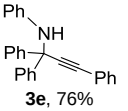
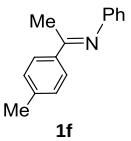
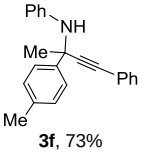
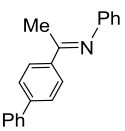
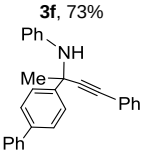
[a] Reaction conditions: **1a** (1 mmol, 195 mg), **2a** (1 or 1.5 mmol), KOBu^t (0.2-1 mmol), DMSO (3 mL); [b] Molar ratio; [c] Isolated yield after column chromatography (SiO_2, *n*-hexane/ethyl acetate, 50:1).

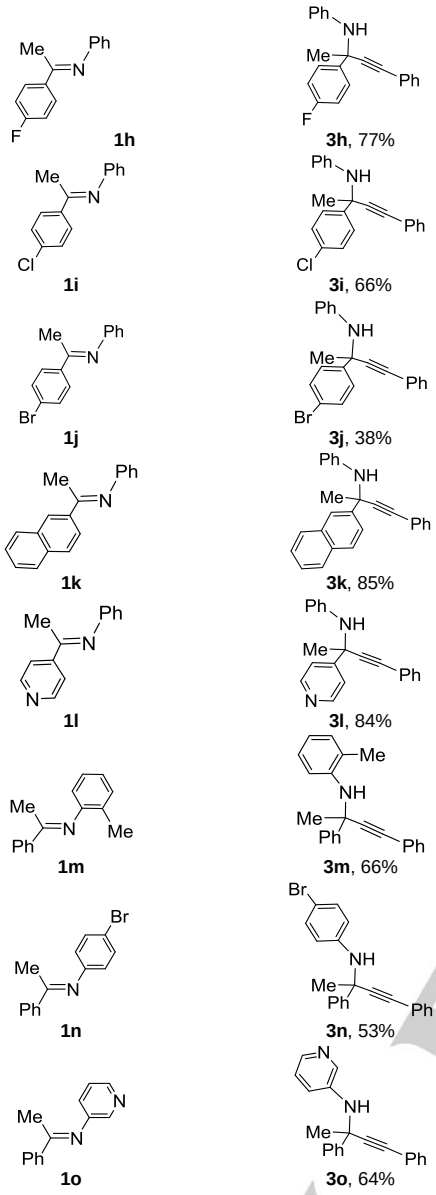
Thus, with these provisionally optimum conditions for implementation of the synthesis, we have investigated the substrate scope of the reaction, first changing ketimine **1** structure and retaining phenylacetylene **2a** as a reference (Table 3).[15]

Table 3. The effect of ketimine structure on the yield of propargylamine **3b-o** in the reaction of ketimines **1b-o** with acetylene **2a**.[a]



1b-o **2a** **3b-o**

Imine **1**	Product, yield[b]
 **1b**	 **3b**, 96%
 **1c**	 **3c**, 80%
 **1d**	 **3d**, 73%
 **1e**	 **3e**, 76%
 **1f**	 **3f**, 73%
 **1g**	 **3g**, 78%



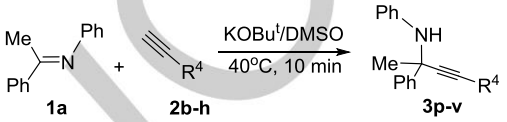
[a] Reaction conditions: **1** (1 mmol), **2a** (1.5 mmol, 153 mg), KOBu^t (0.5 mmol, 56 mg), DMSO (3 mL), 40^{o}C, 10 min; [b] Isolated yield (column chromatography, SiO_2, *n*-hexane/ethyl acetate, 50:1).

As follows from Table 3, the synthesis is efficiently extendable over a great diversity of ketimines derived from aliphatic, cycloaliphatic, aromatic and heteroaromatic ketones. The yields range 64-96% with no evident regularities of the substituents effect. Apparently, the latter is a combination of mutually dependent factors: steric, inductive, conjugative and propensity for auto-condensation. The decreased yield (38 and 53%) for bromosubstituted ketimines **1j,n** is likely due to solvolysis of bromine atom under the action of the KOBu^t/DMSO system, which, besides, results in quenching of its catalytic activity. Certainly, to reach a higher yield for each ketimine, an additional tuning of the reaction conditions is required.

The experiments with ketimines having methyl, allyl and benzyl substituents at the nitrogen atom have shown that while in the former case, the starting ketimine was completely recovered, in the two latter cases, mixtures of products, containing no the expected propargylamines, were formed. Obviously, the donor effect of the methyl substituent depolarizes the C=N bond, thereby decreasing its electrophilicity and, hence, retarding nucleophilic addition of acetylenic carbanion. As to the allyl and benzyl substituents, their active methylene groups likely participate in the adverse proton transfers.

The scope of acetylene substrates **2** has been examined for the reference ketimine **1a** (Table 4).

Table 4. The effect of acetylene structure on the yield of propargylamine **3p-v** in the reaction of ketimine **1a** with acetylenes **2b-n**.[a]



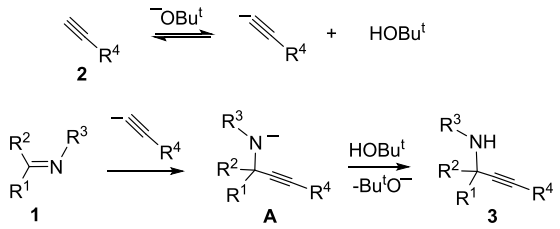
Acetylene **2**	Product, yield[b]
2b	**3p**, 79%
2c	**3q**, 52%
2d	**3r**, 83%
2e	**3s**, 62%
2f	**3t**, 81%
2g	**3u**, 76%
2h	**3v**, 84%

[a] Reaction conditions: **1a** (1 mmol, 195 mg), **2** (1.5 mmol), KOBu^t (0.5 mmol, 56 mg), DMSO (3 mL), 40^{o}C, 10 min; [b] Isolated yield (column chromatography, SiO_2, *n*-hexane/ethyl acetate, 50:1).

The experiments have shown that the reaction tolerates a large series of aryl- and hetarylacetylenes with donor and acceptor substituents, the yields of propargylamines **3p-v** being 52-84%. In this case, the steric effect seems to be more pronounced and is likely the major cause of a lower yield in case of acetylene **2c** (R^4 = 4-PhC_6H_4).

From the reaction of ketimine **1a** with *tert*-butylacetylene and cyclohexylacetylene under the same conditions, only the latter was almost completely recovered (93-95%), whereas no the starting acetylenes were detected in the crude product.

Generally, for the whole reaction the integral substituent effect is in keeping with the mechanism of the process as a nucleophilic addition to the polarized C=N bond (Scheme 2).



Scheme 2. Tentative mechanism.

Indeed, formation of the tetrasubstituted carbon centre (intermediate **A**), resulted from the initial nucleophilic attack of the acetylenic carbanion at C(sp^2) atom, should be sterically hindered, while the acceptor substituents, both in ketimine and acetylene, should facilitate the process, particularly by distribution of negative charge at the nitrogen atom in the intermediate **A** and by increasing concentration of the acetylide anions.

To conclude, the transition metal-free facile (40°C, 10 min) synthesis of secondary propargylamines in good to excellent yields by KOBu^t/DMSO-catalyzed addition of acetylenes to ketone-derived imines has been developed. The synthesis provides a short-cut to a series of propargylamines, hardly accessible via transition metal-catalyzed A^3 condensation.

Acknowledgement

We thank the Baikal Analytical Centre for collective use of the Siberian Branch of the Russian Academy of Sciences for the equipment.

Keywords: ketimines • acetylenes • propargylamines • superbases • ethynylation

[1] For selected examples, see: a) *Acetylene Chemistry. Chemistry, Biology and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), WILEY-VCH, Weinheim, **2005**, pp. 125-130; b) *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations* (Eds.: C.-J. Li, B. M. Trost), Wiley-VCH, Weinheim, **2015**, pp. 239-265; c) K. Lauder, A. Toscani, N. Scalacci, D. Castagnolo, *Chem. Rev*. **2017**, *117*, 14091−14200; d) T. K. Saha, R. Das, *ChemistrySelect* **2018**, *3*, 147–169; e) E. Vessally, M. Babazadeh, A. Hosseinian, L. Edjlali, L. Sreerama, *Curr. Org. Chem*. **2018**, *22*, 199-205.

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[6] For selected examples, see: a) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev*. **2012**, *41*, 3790-3807; b) Y. Liu, *ARKIVOC* **2014**, *i*, 1-20; c) D. Seidel, *Org. Chem. Front*. **2014**, *1*, 426–429.

[7] For selected examples, see: a) A. Grirrane, E. Alvarez, H. García, A. Corma, *Angew. Chem. Int. Ed*. **2014**, *53*, 7253–7258; b) H.-B. Chen, Y. Zhao, Y. Liao, *RSC Adv*. **2015**, *5*, 37737–37741; c) A. M. Munshi, M. Shi, S. P. Thomas, M. Saunders, M. A. Spackman, K. S. Iyer, N. M. Smith, *Dalton Trans.* **2017**, *46*, 5133-5137; d) J. R. Cammarata, R. Rivera, F. Fuentes, Y. Otero, E. Ocando-Mavárez, A. Arce, J. M. Garcia, *Tetrahedron Lett.* **2017**, *58*, 4078-4081; e) V. S. Kashid, M. S. Balakrishna, *Catal. Comm.* **2018**, *103*, 78-82; f) J.-Y. Zhang, X. Huang, Q.-Y. Shen, J.-Y. Wang, G.-H. Song, *Chin. Chem. Lett.* **2018**, *29*, 197-200. g) S. A. Shehzadi, A. Saeed, F. Lemière, B. U. W. Maes, K. A. Tehrani, *Eur. J. Org. Chem*. **2018**, 78–88.

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[15] See the Supporting Information for full experimental details, compounds characterization data, and copies of NMR spectra.

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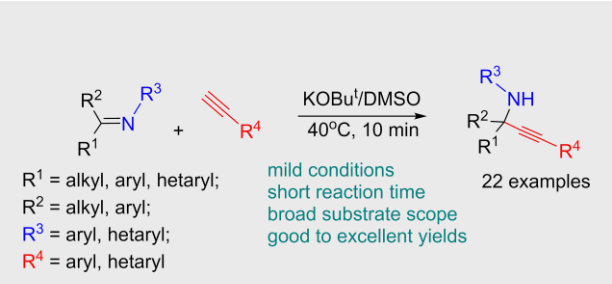

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Superbase-Catalyzed Synthesis of Propargylamines from Ketimines and Acetylenes