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Alexandre Quelhas, Houda Gazzeh, Thierry Roisnel, Yann Trolez, Jean-Claude Guillemin. Passerini and Ugi Reactions Involving Kinetically Unstable Isocyanides. *European Journal of Organic Chemistry*, 2021, 2021 (44), pp.6002-6005. 10.1002/ejoc.202100787 . hal-03414049

HAL Id: hal-03414049

<https://hal.science/hal-03414049>

Submitted on 22 Nov 2021

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Passerini and Ugi reactions involving kinetically unstable isocyanides

Alexandre Quelhas,^[a] Houda Gazzeh,^[a,b] Thierry Roisnel,^[a] Yann Trolez,^[a] Jean-Claude Guillemin^{1* [a]}

Dedicated to the memory of Prof. François Diederich

Abstract: Kinetically unstable isocyanides as vinyl, allenyl and propargyl isocyanides react in Passerini and Ugi reactions faster than they decompose and lead to functionalized α -acyloxy amides and α -amino amides, respectively, which can subsequently be used in reactions involving the unsaturated substituent.

Passerini^[1] and Ugi^[2] reactions are multi-component reactions (MCRs) leading to complex products *via* fast, efficient and convergent pathways. The former involves an isocyanide, an aldehyde (or a ketone) and a carboxylic acid to form α -acyloxy amides while the latter leads to α -amino amides because a primary amine is added to the starting mixture. α -Amino amides have found many applications: they are widely used as a ligand in organometallic chemistry,^[3-6] as extraction agents,^[7] and as building blocks to access a wide range of more complex compounds^[8-12] among which numerous showed a biological activity.^[13-16] Such reactions are usually performed with kinetically stable isocyanides like alkyl and aryl derivatives but esters, amides and even substituted alkenes can also be found as substituents on the starting isocyanides.^[1,2] The introduction of a functional group *via* the substituent on the isocyanide allows increasing the synthetic potentiality of the product if the presence of this group does not disrupt the MCR.^[17] Even if MCRs have been reported with kinetically stable alkenylisocyanides,^[18] such reactions have never been performed with kinetically unstable compounds

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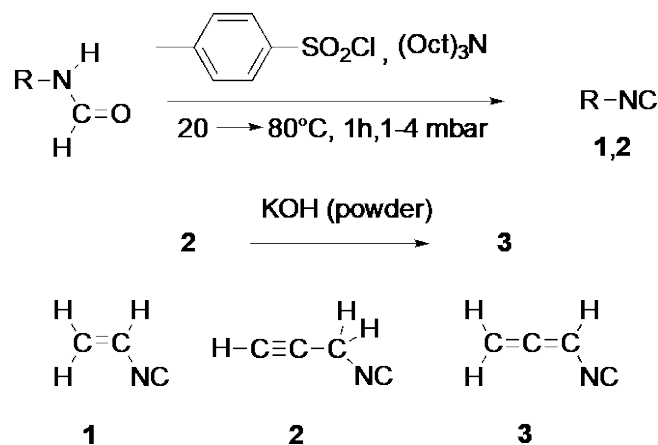
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Supporting information for this article is available on the WWW under <https://doi.org/XXXXX/ejoc.XXXXX>.

like the simplest vinyl (**1**), propargyl (**2**) and allenyl (**3**) isocyanides, three under-investigated isocyanides in organic synthesis (Scheme 1).

We report here Passerini and Ugi reactions using isocyanides **1-3** and, thanks to the presence of this unsaturated group in the products, some of them were involved in ene-thiol, Sonogashira or copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC), featuring the great interest in organic chemistry of such compounds.



Scheme 1. Synthesis of isocyanides **1-3**.

Isocyanides **1-3** were prepared as reported in the literature.^[19] Vinyl and propargyl isocyanides are not stable enough to be kept in pure form in a freezer (− 30 °C) for several days. The allenyl derivative was described as a very unstable compound which decomposes even under dinitrogen atmosphere at − 40 °C and which undergoes explosive polymerization at room temperature.^[20] Isocyanides **1-3** were kept in a Dewar containing dry ice or liquid nitrogen.

Ugi and Passerini reactions have been performed with compounds **1-3** (Tables 1-2). For Ugi reactions, the syntheses were performed in methanol or in water with acetic acid, formaldehyde using tert-butylamine (compounds **4a-c**) (Table 1, entries 1-5) or allylamine (compounds **4d,e**) (Table 1, entries 6,7) as primary amines. Passerini reactions were carried out in the presence of formaldehyde and acetic acid in dichloromethane (compounds **5a-c**) (Table 2). Importantly, when using propargyl isocyanide **2**, we could not avoid the side-formation of a few percent of the allenyl isomer, the amine probably acting as a base to induce a partial isomerization of the isocyanide. Except both reactions in water, the yield ranges from 38 to 62%, slightly lower than yields usually obtained with kinetically stable isocyanides. Although better yields in water than in organic solvents have already been reported for Ugi reactions,^[21] we attributed the lower yields (12 to 18%) we obtained using water as solvent to a low solubility of isocyanides in water. Hence, using water induced high local concentrations of isocyanide in the reaction mixture that led to decomposition faster than in an organic solvent. Compounds **4a-e**, **5a-c** were characterized by NMR spectroscopy and high-resolution

mass spectrometry. Cis and Trans rotamers in a ratio 4:6 respectively were observed for compounds **4d** and **4e**. They were unambiguously characterized and distinguished thanks to NOESY experiments (Figures S9 and S12). Variable temperature ^1H NMR experiments were performed on compound **4d** in DMSO- d_6 (Figure 1). Coalescence of all the signals was observed at 373 K. After this experiment, the sample was cooled to room temperature and a new ^1H NMR spectrum was recorded 3 hours 40 minutes later at the initial temperature (296 K). All the signals were back as in the first recorded spectrum before heating, in the same ratio (4:6).

Table 1. Ugi MCRs with vinyl- **1**, propargyl- **2** and allenylisocyanide **3**.

<p>1, 4a: R = 2, 4b: R = 3, 4c: R = </p>				
Entry	Isocyanide	Solvent	Product	Yield (%)
1 ^[a]	1	MeOH	4a	49
2 ^[a]	1	Water	4a	12
3 ^[a]	2	MeOH	4b	50
4 ^[a]	2	Water	4b	18
5 ^[a]	3	MeOH	4c	38
<p>1, 4d: R = 2, 4e: R = </p>				
Entry	Isocyanide	Solvent	Product	Yield (%)
6 ^[b]	1	MeOH	4d	31
7 ^[b]	2	MeOH	4e	39
^[a] <i>t</i> -butylamine (1 equiv.), Formaldehyde (37%) (1 equiv.), AcOH (1 equiv.). ^[b] Allylamine (1 equiv.), Formaldehyde (37%), (1 equiv.), AcOH (1 equiv.) MeOH.				

Table 2. Passerini MCRs with vinyl- **1**, propargyl- **2** and allenylisocyanide **3**.

$\text{H}-\text{C}(=\text{O})-\text{H} + \text{H}_3\text{C}-\text{C}(=\text{O})-\text{OH} + \text{R}-\text{NC} \longrightarrow \text{O}=\text{C}(\text{CH}_3)-\text{O}-\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{R}$ <p style="text-align: center;">5a-5c</p> <p> 1, 5a: R = , 2, 5b: R = H-, 3, 5c: R = </p>			
Entry	Isocyanide	Product	Yield (%)
8 ^[a]	1	5a	45
9 ^[a]	2	5b	41
10 ^[a]	3	5c	62
^[a] Formaldehyde (37%) (4 equiv.), AcOH (1 equiv.), CH ₂ Cl ₂ .			

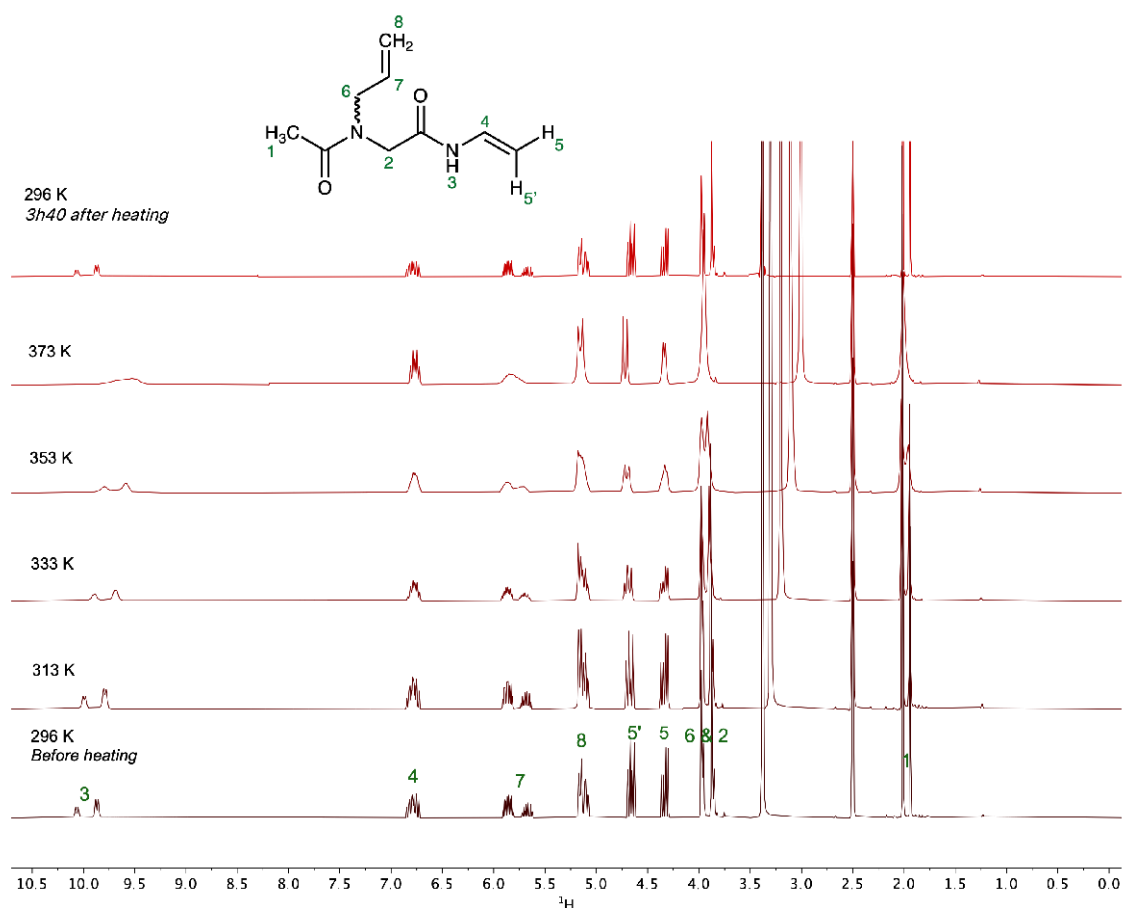
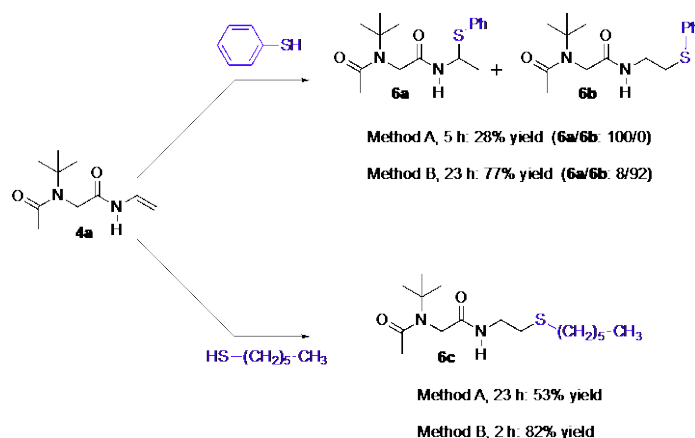
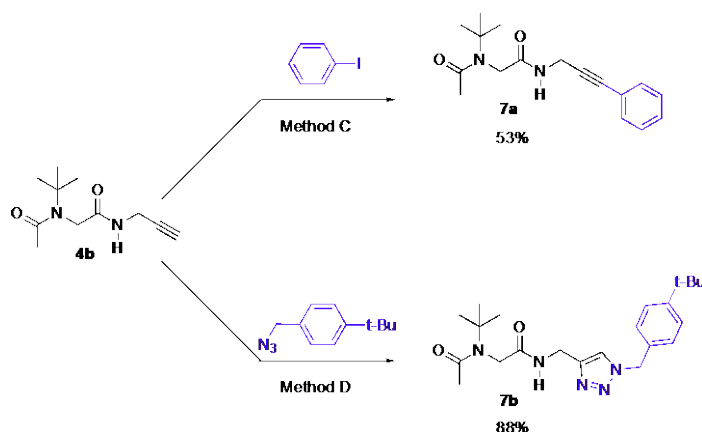


Figure 1. Stacked ¹H NMR spectra (400 MHz, DMSO-d₆) of (**4d**) recorded at five different temperatures (296 K, 313 K, 333 K, 353 K and 373 K).

Products **4a** and **4b** were investigated in some reactions involving the unsaturated group (Schemes 2,3). Ene-thiol reactions with compound **4a** gave the corresponding sulfide **6a-6c** in moderate to good yields. In the presence of a base (piperidine), only product **6a** was isolated while the major product is the other regioisomer **6b** in the absence of base. Such a behavior leading to the Markovnikov-type product has already been observed in the presence of Pd catalyst^[22] or under irradiation.^[23] With the 1-hexanethiol, only the product corresponding to an anti-Markovnikov-type product **6c** was observed in the presence or absence of base. We attributed these differences to acid-base interactions between the piperidine and thiophenol, a thiol more acidic than 1-hexanethiol. Compound **4b** which comes from the propargyl isocyanide **2** was reacted in a Sonogashira coupling with iodobenzene to give the expected product **7a** in 45% yield. After a copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC), compound **4b** and para-t-butylbenzylazide led to the corresponding 1,2,3-triazole **7b** in a very good yield (88%).



Scheme 2. Subsequent reaction on the unsaturated moiety of compound **4a**. Method A: **4a**, thiol (1.1 equiv.), piperidine (2 drops), dioxane, reflux. Method B: **4a**, thiol (1.1 equiv.), dioxane, reflux.



Scheme 3. Subsequent reactions on the unsaturated moiety of compound **4b**. Method C: **4b**, iodobenzene (2 equiv.), CuI (16%), PdCl₂(PPh₃)₂ (8%), PPh₃ (16%), THF, reflux. Method D: **4b**, para-t-butylbenzylazide (1 equiv.) CuI (1%), PPh₃ (2%), DIPEA (3 equiv.), toluene, reflux.

In addition to usual spectroscopic characterizations, the X-ray structure of compounds **4d**, **6a** and **7b** could be solved (Figure 3). CCDC 2088057 (for **4d**), 2054094 (for **6a**) and 2054093 (for **7b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre. They have a similar conformation where the two C=O double bonds are not standing in the same plane. They are folded so that compound **7b** shows a basket-like shape where the two t-butyl groups are standing next to each other (the shortest distance between two carbon atoms of these groups is about 4.0 Å).

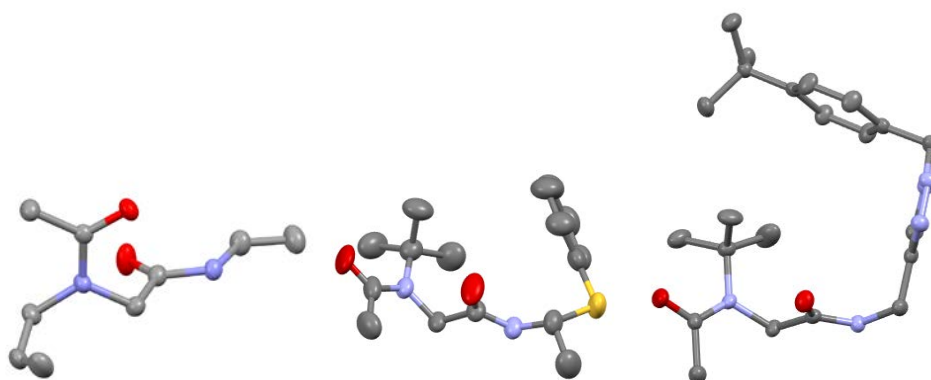


Figure 3. X-ray structure of compounds **4d** (left), **6a** (middle) and **7b** (right). Hydrogen atoms are omitted for clarity; ellipsoids are drawn with 50% probability.

Diluted in an organic solvent, simple α,β -unsaturated isocyanides **1-3** are stable enough to be involved in Passerini and Ugi reactions to lead to the expected product in moderate yields. Thanks to the presence of the unsaturated substituent on the nitrogen, a subsequent reaction gives access to more sophisticated compounds showing that such unsaturated and kinetically unstable isocyanides **1-3** are powerful tools in synthetic organic chemistry. The synthesis of unsaturated derivatives of biomolecules and those formed by a subsequent reaction on the unsaturated group are currently under progress in our lab.

Acknowledgments

The Centre National d'Etudes Spatiales (CNES) is gratefully acknowledged for financial support. AQ is grateful for the Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Kinetically Unstable Isocyanides • Multicomponent Reaction • Passerini Reaction • Ugi Reaction

- [1] a) L. Banfi, R. Riva, *R. Org. React.* **2005**, *65*, 1–140. b) V. G. Nenajdenko, *Isocyanide Chemistry: Applications in Synthesis and Material Science*, Wiley-VCH, Weinheim, **2012**. c) S. S. van Berkel, B. G.M. Boegels, M. A. Wijdeven, B. Westermann, F. P. J. T. Rutjes, *Eur. J. Org. Chem.*, **2012**, 3543–3559.
- [2] a) I. Ugi, S. Lohberger, R. Karl, in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, 1083. b) L. A. Polindara-García, E. Juaristi, *Eur. J. Org. Chem.*, **2016**, 1095–1102. c) A. Domling, Y. Huang, *Synthesis* **2010**, 2859–2883. d) S. Sadjadi, M. M. Heravi, *Tetrahedron* **2011**, *67*, 2707–2752.
- [3] A. V. Kharcheva, D. A. Evdokimov, M. D. Reshetova, V. I. Yuzhakov, S. V. Patsaeva, N. E. Borisova, *Mendeleev Communications* **2017**, *27*, 459–461.
- [4] Y. Pérez, A. L. Johnson, P. R. Raithby, *Polyhedron* **2011**, *30*, 284–292.
- [5] R.-R. Tang, G.-L. Gu, Q. Zhao, *Spectroc. Acta A* **2008**, *71*, 371–376.
- [6] N. Kumar, M. D. Milton, J. D. Singh, S. Upreti, R. J. Butcher, *Tetrahedron Lett.* **2006**, *47*, 885–889.
- [7] E. Makrlík, P. Vaňura, P. Selucký, V. Babain, M. Alyapyshev, D. Dar'in, *J. Mol. Liq.* **2017**, *237*, 490–495.
- [8] S.-H. Hsiao, J.-S. Han, *Eur. Polym. J.* **2017**, *90*, 122–135.
- [9] J. S. Dhau, R. Dhir, A. Singh, A. Singh, P. Brandão, V. Félix, *Tetrahedron* **2014**, *70*, 4876–4883.
- [10] R. M. B. Carrilho, M. M. Pereira, M. J. S. M. Moreno, A. Takács, L. Kollár, *Tetrahedron Lett.* **2013**, *54*, 2763–2765.
- [11] M. Kiss, N. Pálkás, A. Takács, S. Mahó, L. Kollár, *Steroids* **2013**, *78*, 693–699.
- [12] M. Porcs-Makkay, B. Volk, Z. Mucsi, G. Simig, *Tetrahedron* **2010**, *66*, 7017–7027.
- [13] S. Zhou, S. Zhou, Y.-T. Xie, R.-Y. Jin, X.-D. Meng, D.-K. Zhang, X.-W. Hua, M. Liu, C.-C. Wu, L.-X. Xiong, Y. Zhao, Z.-M. Li, *Chin. Chem. Lett.* **2017**, *28*, 1499–1504.
- [14] S. Mert, Z. Alim, M. M. İsgör, Ş. Beydemir, R. Kasımoğulları, *Bioorg. Chem.* **2016**, *68*, 64–71.
- [15] M. Saudi, J. Zmurko, S. Kaptein, J. Rozenski, J. Neyts, A. Van Aerschot, *Eur. J. Med. Chem.* **2014**, *87*, 529–539.
- [16] C. A. Van Huis, A. Casimiro-Garcia, C. F. Bigge, W. L. Cody, D. A. Dudley, K. J. Filipski, R. J. Heemstra, J. T. Kohrt, R. J. Leadley, L. S. Narasimhan, T. McClanahan, I. Mochalkin, M. Pamment, J. Thomas Peterson, V. Sahasrabudhe, R. P. Schaum, J. J. Edmunds, *Bioorg. Med. Chem.* **2009**, *17*, 2501–2511.
- [17] P. Patil, M. Ahmadian-Moghaddam, A. Dömling, *Green Chem.* **2020**, *22*, 6902–6911.
- [18] M. C. Pirrung, S. Ghorai, *J. Am. Chem. Soc.* **2006**, *128*, 11772–11773.

- [19] A. Chrostowska, A. Matrane, D. Maki, S. Khayar, H. Ushiki, A. Graciaa, L. Belachemi, J.-C. Guillemin, *ChemPhysChem* **2012**, *13*, 226–236.
- [20] J. W. Zwikker, R. W. Stephany, *Synth. Comm.* **1973**, *3*, 19–23.
- [21] M. C. Pirrung, K. D. Sarma, *J. Am. Chem. Soc.* **2004**, *126*, 444–445.
- [22] T. Tamai, A. Ogawa, *J. Org. Chem.* **2014**, *79*, 5028–5035.
- [23] E. Barman, J. Hourezadeh, D. Lim, *Tetrahedron Lett.* **2020**, *61*, 152201.

Table of Content

The kinetically unstable vinyl, allenyl and propargyl isocyanides were reacted under the conditions of Passerini and Ugi reactions. They led to α -acyloxy amides and α -amino amides with an unsaturated substituent on the nitrogen atom in reasonable yields. Some of them were then functionalized thanks to the pending unsaturation, opening the field of complex products in subsequent reactions.

