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Isocyanides and Arylacetic Acids: Synthesis and Reactivity of 3-Aryl-2-acyloxyacrylamides, an Example of Serendipity-Oriented Synthesis

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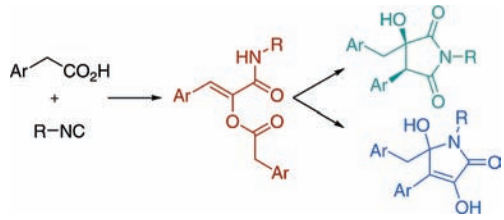
ABSTRACT



Research progress is often promoted by unexpected results that open the way to new scenarios. In this communication, an unprecedented condensation of arylacetic acids and isocyanides and the unusual base-mediated rearrangement of the resulting products to give two novel classes of polysubstituted pyrrolones and pyrrolidinediones are reported.

Isocyanide-based reactions are among the most popular multicomponent condensations. Such reactions include the famous Passerini and Ugi ones, both involving a nucleophile (a carboxylic acid) and an electrophile (an aldehyde or imine, respectively) reacting with the divalent carbon of the isocyanide.[1]

Our research group has been involved for several years in searching for variations of such multicomponent reactions leading to molecular scaffolds different from the classic depsipeptides and peptides.[2] In one of our research programs, we attempted to perform a Passerini reaction with 1*H*-pyrrole-2-carboxaldehyde as the carbonyl component. The reaction was performed with various carboxylic acids and isocyanides under different conditions but never gave the desired product, probably confirming the vinylogous amide character of this aldehyde; however, when the reaction was conducted with phenylacetic acid and cyclohexyl isocyanide under microwave heating (100 °C for 30 min), a product **1a** that did not incorporate the carbonyl derivative was isolated in high yield. Intrigued by this outcome, we performed the reaction under the same conditions but without the aldehyde, and NMR and GC-MS analysis of the crude showed formation of equimolar amounts of **1a** and *N*-cyclohexyl formamide. The formula of **1a** corresponds to the inclusion of two molecules of phenylacetic acid and one of isocyanide with the loss of one molecule of water which is included in the second equivalent of

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(1) For reviews, see, for example: (a) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321–3329. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(2) See, for example: (a) Basso, A.; Banfi, L.; Guanti, G.; Riva, R. *Org. Biomol. Chem.* **2009**, *7*, 253–258. (b) Banfi, L.; Basso, A.; Guanti, G.; Kielland, N.; Repetto, C.; Riva, R. *J. Org. Chem.* **2007**, *72*, 2151–2160. (c) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron* **2006**, *62*, 8830–8837. Basso, A.; Banfi, L.; Guanti, G.; Riva, R.; Riu, A. *Tetrahedron Lett.* **2004**, *45*, 6109–6111.

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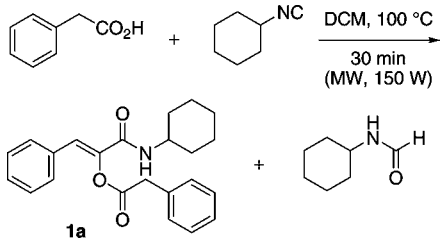
the isocyanide, and its structure was the captodative olefine **1a** (Scheme 1).[3,4]

Scheme 1. Reaction between Phenylacetic Acid and Cyclohexylisocyanide



Danishefsky recently reported the sequential concerted rearrangement mechanism occurring in the coupling between isocyanides and carboxylic acids, leading to *N*-formylamides.[5] The different outcome observed when the carboxylic derivative is a phenylacetic acid prompted us to disclose our results.

Compounds with general formula **1** (Figure 1) are very rarely reported in the literature, if we exclude their synthesis starting from α-acetoxycinnamoyl chloride[6] and a report by I. Ugi[7] where compound **3** is obtained by treatment of compound **2** with concentrated HCl. Compound **2**, on the other hand, is obtained by reaction of an isocyanide with 2 equiv of diphenylketene. The reactivity of isocyanides with ketenes, investigated for the first time by Ugi[8] and reported also by Moore[9] and Robertson,[10] gave us some hints about the mechanism of this novel reaction.

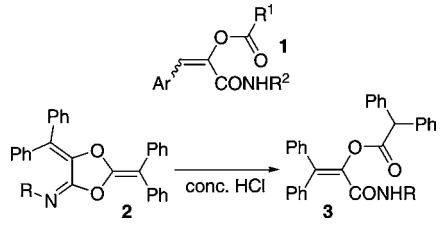


Figure 1. Early report by I. Ugi.

In our hypothesis, phenylacetic acid and isocyanide react to give α-addition adduct **a**; however, this mixed anhydride does not evolve via a 1,3-acyl shift to give **b** as described by Danishefsky but reacts with an additional molecule of isocyanide to form **c** and anionic formamide **d** (Scheme 2), neutralized by the excess acid, in analogy with the Nef reaction[11] where an acyl chloride undergoes an α-addition on an isocyanide. Formation of intermediate **c** in our case should be favored by the equilibrium with tautomer **e**, stabilized by extensive conjugation with the aromatic ring; formation of **e** has already been described by Robertson in the reaction of a molecule of ketene with one of isocyanide. Compound **e** then reacts with another molecule of phenylacetate to give **f** and finally **1** via a sort of Mumm rearrangement. According to this hypothesis, the different outcome of arylacetic acids compared to other carboxylic compounds should be related to the higher tendency to give intermediate **e**. It is worth noting that other acetic acid derivatives, lacking a conjugating substituent, failed to give this reaction, behaving mostly as described by Danishefsky. In principle, other mechanisms could not be ruled out, for example, the direct formation of a ketene from **a** with a E1cb elimination and its subsequent reaction with a molecule of acid and one of isocyanide, in a way similar to that reported by Ugi, although the absence of a base catalysis makes this hypothesis less likely.[12] Also, formation of a symmetrical anhydride[13] from **a** and an additional molecule of acid could be in principle possible, and indeed when we investigated the reaction of phenylacetic anhydride with 0.5 equiv of cyclohexyl isocyanide compound **1** was isolated (in this case, without formation of the formamide) although in lower yields.

We have also investigated the influence of the relative ratio of reagents, the temperature, and the solvent, as outlined in Table 1. These experiments clearly indicated that the stoichiometry of the reaction involves 2 equiv of acid and 2 equiv of isocyanide to give 1 equiv of **1** and 1 equiv of formamide. It is worth noting that under the same conditions described by Danishefsky (entry d) the reaction was complete after 1 min, while formation of *N*-formylamides usually required 30 min. Moreover, the reaction proceeded well also with conventional heating (entry g), although being much slower.

Table 1. Analysis of Different Reaction Conditions

entry	isocyanide/ acid ratio	temp (°C)	solvent	yield[a]
a	1:1	100 (30 min)	DCM	85
b	1:2	100 (30 min)	DCM	45
c	2:1	100 (30 min)	DCM	78
d	1:1	150 (1 min)	DCM	94
e	1:1	100 (30 min)	THF	75
f	1:1	100 (30 min)	*t*-BuOH	50
g	1:1	reflux, o/n[b]	DCE	84

[a] Based on the amount of acid. [b] Conventional heating in an oil bath.

We subsequently explored the reactivity of various isocyanides and arylacetic acid derivatives under the standard condi-

(3) Several years ago, in our group, adducts with a similar formula had been detected after reaction of phenylacetic acid with isocyanides but were not examined with much attention, and a wrong cyclic structure was assigned at that time and reported in ref 4 at page 14.

(4) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1.

(5) (a) Li, X. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448. (b) Jones, G. O.; Li, X. C.; Hayden, A. E.; Houk, K. N.; Danishefsky, S. J. *Org. Lett.* **2008**, *10*, 4093–4096. (c) Li, X. C.; Yuan, Y.; Berkowitz, W. F.; Todaro, L. J.; Danishefsky, S. J *J. Am. Chem. Soc.* **2008**, *130*, 13222–13224. (d) Li, X. C.; Yuan, Y.; Kan, C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13225–13227.

(6) Chigira, Y.; Masaki, M.; Ota, M. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 228–232.

(7) El Gomati, T.; Firl, J.; Ugi, I. *Chem. Ber.* **1977**, *110*, 1603–1605.

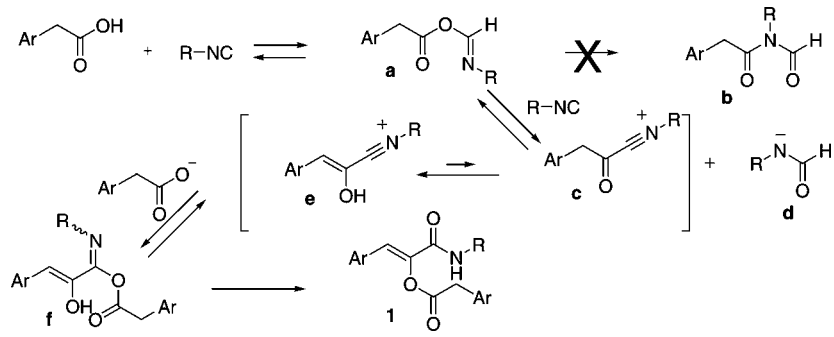
(8) Ugi, I.; Rosendahl, K. *Chem. Ber.* **1961**, *94*, 2233–2235.

(9) Moore, H. W.; Yu, C.-C. *J. Org. Chem.* **1981**, *46*, 4935–4938.

(10) Robertson, J.; Bell, S. J.; Krivokapic, A. *Org. Biomol. Chem.* **2005**, *3*, 4246–4251.

(11) Ugi, I.; Fetzer, U. *Chem. Ber.* **1961**, *94*, 1116.

Scheme 2. Postulated Mechanism for the Formation of **1**



tions (30 min at 100 °C), finding that the scope of the reaction was quite general and that conversions were generally good (Table 2). The correct assignment of the *Z* configuration of the double bond was made possible by the observation that compounds **1f**, **1g**, **1i**, and **1j** showed NOE between the amidic and the olefinic hydrogens, only possible when the aryl group and the amide are *trans*. However, generalization to all compounds **1** was not possible with this technique since NOEs were not clearly observed for other derivatives (the olefinic hydrogen was often buried within the aromatic region). At this purpose, we analyzed the signal belonging to the carbonyl amide in the coupled ^{13}C NMR spectrum: this was always a triplet, due to the ^{2}J coupling wih the hydrogen NH and the ^{3}J coupling with the olefinic proton, both being constantly between 3 and 4 Hz, consistent with a *cis* configuration between the olefinic hydrogen and the carbonyl amide.[14]

Table 2. Investigation of the Scope of the Reaction

entry	isocyanide	acid	yield (**1**)
a	cyclohexyl	phenylacetic	85%
b	*n*-butyl	phenylacetic	90%
c	*t*-butyl	phenylacetic	76%
d	4-MeO-phenyl	phenylacetic	53%
e	methyl isocyanopropionate	phenylacetic	54%
f	*t*-butyl	3-MeO-phenylacetic	90%
g	*t*-butyl	4-Cl-phenylacetic	88%
h	*n*-pentyl	1-naphthylacetic	51%
i	benzyl	4-Cl-phenylacetic	64%
j	*n*-butyl	4-Cl-phenylacetic	58%
k	*n*-pentyl	2-NO_2-phenylacetic	62%
l	*t*-butyl	2-thiophenylacetic	75%

Compounds of formula **1** can be classified as captodative olefins, which are often employed in cycloaddition reactions.[15,16]

Preliminary attempts to react compound **1b** either with dienes in a Diels−Alder reaction or with nitrones, nitrile oxides, or diazocompounds in 1,3-dipolar cycloadditions failed. However, when the conditions described by Lasri were employed to generate in situ the nitrile oxide, a main product **5b** was formed whose structure derived from the rearrangement of compound **1b**, without inclusion of the nitrile oxide. Postulating that the rearrangement had occurred for the presence of the base used to generate the nitrile oxide, compound **1b** was simply reacted with triethylamine under the same solvent and temperature conditions: indeed the same outcome was observed. We also investigated whether stronger bases would give the same rearrangement at lower temperatures; however, reacting **1b** with NaH or *t*-BuONa at room temperature, a different rearranged product **6b** was isolated. NMR analysis of both compounds highlighted the absence of the amidic hydrogen and the appearance of two diastereotopic benzylic hydrogens, an aliphatic OH, and a quaternary aliphatic carbon. In addition, compound **5b** showed an aliphatic CH and two carbonyls, while compound **6b** showed a tetrasubstituted double bond, an additional OH, more acidic, and only one carbonyl. On the basis of this evidence, the structures of **5b** and **6b** were devised as illustrated in Scheme 3. The coherence between these structures and the observed ^{13}C NMR chemical shifts was first examined by DFT calculations:[17] a linear fit of experimental vs calculated data provided strong correlations with no significant outliers. Additional HMBC experiments were also run, showing crosspeaks due to $^{2}J_{CH}$ and $^{3}J_{CH}$ couplings consistent with the proposed structures. Finally, NOE experiments established the relative configuration of **5b** (see Supporting Information for details).

We postulated that compound **1b**, treated with a base, could give a transacylated adduct that, according to the particular reaction conditions, would cyclize via the aldol condensation of the α-carbon of the phenylacetimide to the carbonyl group in **4b** (to give **5b**) or the attack of the enolate

(12) (a) Cho, B. R.; Kim, N. S.; Kim, Y. K.; Son, K. H. *J. Chem. Soc.-Perkin Trans.* **2000**, *2*, 1419–1423. (b) Cho, B. R.; Kim, Y. K.; Seung, Y. J.; Kim, J. C.; Pyun, S. Y. *J. Org. Chem.* **2000**, *65*, 1239–1242.

(13) Gautier, A. *Ann. Chim. (Paris)* **1869**, *17*, 222.

(14) Rulev, A. Y.; Ushakov, I. A.; Nenajdenko, V. G. *Tetrahedron* **2008**, *64*, 8073–8077.

(15) For Diels−Alder reactions: Herrera, R.; Jiménez-Vàzquez, H. A.; Modelli, A.; Jones, D.; Söderberg, B. C.; Tamariz, J. *Eur. J. Org. Chem.* **2001**, 4657.

(16) For 1,3-dipolar cycloadditions: (a) Herrera, R.; Nagarajan, A.; Morales, M. A.; Mendez, F.; Jiménez-Vàzquez, H. A.; Zepeda, L. G.; Tamariz, J. *J. Org. Chem.* **2001**, *66*, 1252–1263. (b) Lasri, J.; Mukhopadhyay, S.; Charmier, M. A. J. *J. Heterocycl. Chem.* **2008**, *45*, 1385–1389. (c) Nagarajan, A.; Zepeda, G.; Tamariz, J. *Tetrahedron Lett.* **1996**, *37*, 6835–6838.

(17) See, for example: Bagno, A.; Rastrelli, F.; Saielli, G. *Chem.—Eur. J.* **2006**, *12*, 5514–5525.

Scheme 3. Two Alternative Rearrangement Reactions of Compound **1b**

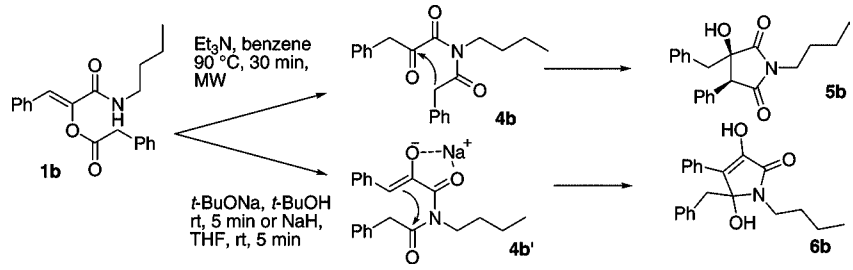


Table 3. Results for the Base-Mediated Rearrangement−Cyclization of Compounds **1**

entry	substrate	type of product	yield
a	**1b**	**5**	60%
b	**1b**	**6**	84%
c	**1e**	**6**	85%
d	**1i**	**6**	65%
e	**1j**	**6**	72%
f	**1a**	**5**	63%

to the imidic carbonyl in **4b′** (to give **6b**). The two alternative mechanisms are exclusive, and formation of **4b′** could be favored by the presence of a chelating metal ion, although more detailed studies will be carried out in due course.

The same reactions were performed with other substrates, to prove the generality of the two methods, and the results are summarized in Table 3.

In conclusion, we have reported a novel outcome of the reaction between isocyanides and carboxylic acids, when the latter is an arylacetic derivative, and we have also investigated the unprecedented reactivity of such enolamide derivatives when treated with bases, leading to two interesting classes of five-membered heterocycles. Further developments will be reported in due course.

Acknowledgment. The authors acknowledge MiUR and Fondazione San Paolo for financial support.

Supporting Information Available: General experimental procedures, full characterization of compounds **1**, **5**, and **6**, DFT analysis, and NMR prediction for compounds **5b** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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