ORGANIC
LETTERS

2010
Vol. 12, No. 3
416−419

Unusual Approach to Branched 3-Alkynylamides and to 1,5-Dihydropyrrol-2-ones

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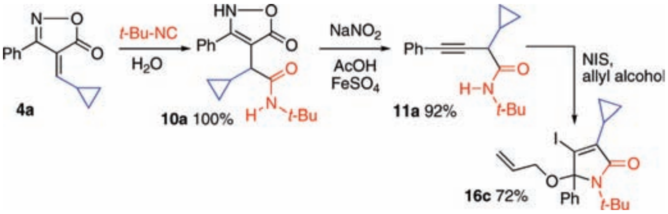
Received October 27, 2009

ABSTRACT



Rare carboxamide branched alkynes such as 11a can be readily obtained by reaction of the electrophilic 4-alkylidene isoxazolinones with isocycanides followed by nitrosative cleavage of the heterocyclic ring. *N*-Iodosuccinimide induced ring closure in the presence of a nucleophile results in the formation of new iodopyrrolinones such as 16c.

The carbon−carbon triple bond is arguably among the two or three most important functional groups in organic synthesis.[1] Its versatility and utility can be gauged by the unabated flow of countless transition metal catalyzed transformations reported in the past decades. Indeed, the recent explosive growth in the development and use of reactions such as the enyne metathesis and gold catalyzed processes is indicative of the central position occupied by alkynes.[2] From this perspective, the design of new routes to alkynes remains a very worthwhile endeavor.

Some years ago, we devised a new synthesis of alkynes **2** starting from β-ketoesters.[3] The method hinges on the nitrosation of the corresponding isoxazolinones **1** (in tautomeric equilibrium with **1′**) by a combination of sodium nitrite and acetic acid in the presence of iron sulfate, as shown in Scheme 1. The iron sulfate is needed to generate nitric oxide *in situ* and thus suppress an unwanted radical side reaction leading to dimers. One aspect of the chemistry of isoxazolinone is the ability of 4-unsubstituted isoxazolinones to undergo Knoevenagel type condensations with aldehydes and ketones **3**, leading to highly electrophilic 4-alkylidene derivatives **4**.[4] These react readily with various nucleophiles, including organometallic reagents, to give conjugate adducts **5**,[3c,f,5] and hence the corresponding branched alkynes **6**. The conversion of 4-benzylidene isoxazolinone **4a**, obtained in quantitative yield by condensation of commercially available isoxazolinone **1a** (**1**, R = Ph, R′ = H) with benzaldehyde, into diyne **6a** by way of adduct **5a** is illustrative of this technology.

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(1) (a) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; Wiley-VCH: Weinheim, 1995. (b) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier Science: New York, 1992. (c) Ben-Efraim, D. A. In *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1978; chap. 18, p 755. (d) Jäger, V. In *Methoden Organic Chemistry (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1977; Vol. 5/2a.

(2) Selected reviews on enyne and alkyne metathesis: (a) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55. (b) Diver, S.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (c) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A. *Chem. Commun.* **1997**, 1375. (d) Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307. (e) Sashuk, V.; Ignatowska, J.; Grela, K. *J. Org. Chem.* **2004**, *69*, 77481. Selected reviews on gold catalysis: (f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (g) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.

(3) (a) Boivin, J.; Elkaim, L.; Ferro, P. G.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 5321. (b) Boivin, J.; Huppé, S.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 5737. (c) Boivin, J.; Huppé, S.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 48–8735. (d) Boutillier, P.; Zard, S. Z. *Chem. Commun.* **2001**, 1304. (e) Huppé, S.; Rezaei, H.; Zard, S. Z. *Chem. Commun.* **2001**, 1894. (f) Renard, D.; Rezaei, H.; Zard, S. Z. *Synlett* **2002**, *8*, 1257. (g) Zard, S. Z. *Chem. Comm.* **2002**, 1555. For an application in the synthesis of odorant cycloalkynes, see: (h) Lehmann, J.; Tochtermann, W. *Tetrahedron* **1999**, *55*, 2639.

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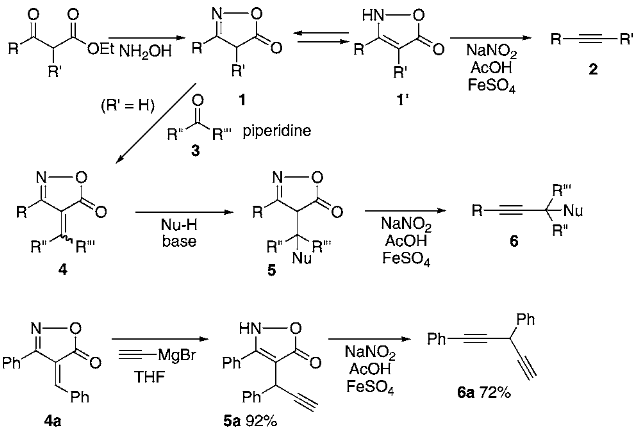
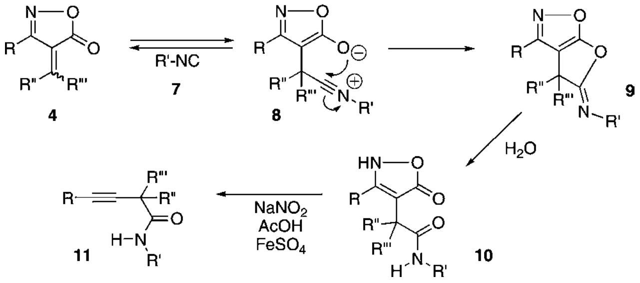
Scheme 1



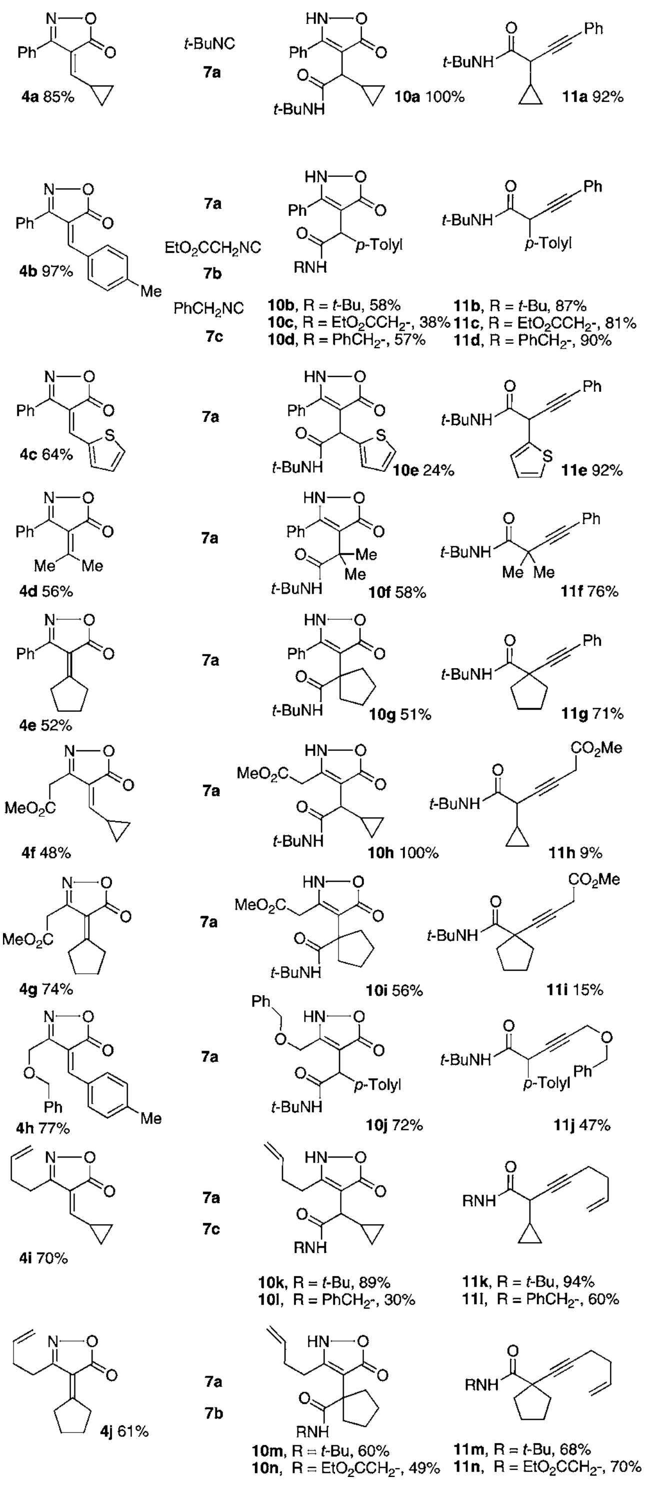
We anticipated that the electrophilicity of the 4-alkylidene isoxazolinones **4** would be sufficiently high to invite a nucleophilic attack by an isonitrile, as depicted in Scheme 2.[6] While this nucleophilic attack leading to intermediate **8** is expected to be reversible, the ring closure of the carbonyl oxygen on the incipient iminium ion would furnish **9**, the hydrolysis of which would result in the irreversible formation of amide **10**. Nitrosative cleavage of the isoxazoline ring would finally provide the desired alkynylamide **11**. Such alkynylamides are relatively uncommon as they are not readily accessible by classical routes.[7]

Scheme 2



The first reactions were studied starting with commercially available isoxazolinone **1a** (**1**, R = Ph, R′ = H). As summarized in Table 1, condensation with cyclopropanecarboxaldehyde in the presence of piperidine furnished the corresponding 4-alkylidene isoxazolinone **4a** in 85% yield.

Table 1. Formation of Carboxamide Branched Alkynes **11**



Isoxazolidinone 4	Isocyanide 7	Amide 10	Alkynylamide 11
4a 85%	*t*-BuNC **7a**	**10a** 100%	**11a** 92%
4b 97%	**7a** EtO$_2$CCH$_2$NC **7b** PhCH$_2$NC **7c**	**10b**, R = *t*-Bu, 58% **10c**, R = EtO$_2$CCH$_2$-, 38% **10d**, R = PhCH$_2$-, 57%	**11b**, R = *t*-Bu, 87% **11c**, R = EtO$_2$CCH$_2$-, 81% **11d**, R = PhCH$_2$-, 90%
4c 64%	**7a**	**10e** 24%	**11e** 92%
4d 56%	**7a**	**10f** 58%	**11f** 76%
4e 52%	**7a**	**10g** 51%	**11g** 71%
4f 48%	**7a**	**10h** 100%	**11h** 9%
4g 74%	**7a**	**10i** 56%	**11i** 15%
4h 77%	**7a**	**10j** 72%	**11j** 47%
4i 70%	**7a** **7c**	**10k**, R = *t*-Bu, 89% **10l**, R = PhCH$_2$-, 30%	**11k**, R = *t*-Bu, 94% **11l**, R = PhCH$_2$-, 60%
4j 61%	**7a** **7b**	**10m**, R = *t*-Bu, 60% **10n**, R = EtO$_2$CCH$_2$-, 49%	**11m**, R = *t*-Bu, 68% **11n**, R = EtO$_2$CCH$_2$-, 70%

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(4) (a) Lang, S. A.; Lin, Y.-I. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 6, pp 103−105. (b) Boulton, A. J.; Katritzky, A. R. *Tetrahedron* **1961**, *12*, 41. (c) Wollweber, H. G.; Wentrup, C. *J. Org. Chem.* **1985**, *50*, 2041, and references cited therein.

(5) (a) Mustafa, A.; Asker, W.; Harhash, A. H.; Kassab, N. A. L.; Elnagdi, M. H. *Tetrahedron* **1964**, *20*, 1133. (b) Mustafa, A.; Asker, W.; Harhash, A. H.; Kassab, N. A. L. *Tetrahedron* **1963**, *19*, 1577.

(6) For recent reviews on isocyanides in multicomponent reactions, see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Orru, R. V. A.; Greef, M. *Synthesis* **2003**, 1471. (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321. (d) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. For a very recent application, see: . (e) Shaabani, A.; Soleimani, E.; Rezayan, A. H.; Sarvary, A.; Khavasi, H. R. *Org. Lett.* **2009**, *11*, 3342.

(7) (a) Takahashi, K.; Midiro, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244. (b) Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2687. (c) Nussbaumer, P.; Leitner, I.; Mraz, K.; Stütz, A. *J. Med. Chem.* **1995**, *38*, 1831.

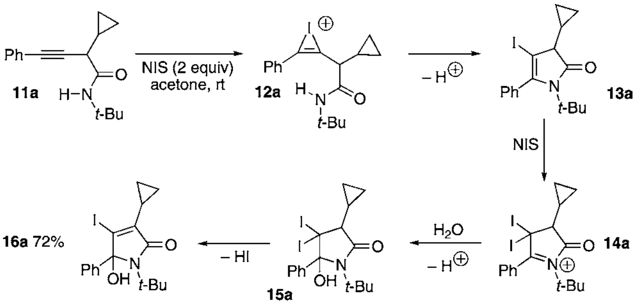
Heating with *t*-butyl isocyanide **7a** afforded the expected amide **10a** in quantitative yield. Other aldehydes such as *p*-tolualdehyde and thiophene-2-carboxaldehyde could be used, as well as ketones such as acetone and cyclopentanone. As for the isocyanides, *t*-butyl isocyanide **7a** gave generally the best results. Yields with ethyl isocyanoacetate **7b** and benzyl isocyanide **7c** tended to be significantly lower. Modifications in the isoxazolinone partner **1** could be readily introduced as illustrated by the obtention of compounds **4f−i** and their conversion into amides **11h−n**.

Having established a convenient access to branched isoxazolinyl amides, their conversion to the corresponding alkynes was next attempted. We were concerned by the possible formation of *N*-nitrosoamides by nitrosation of the amide group under the nitrosating conditions. This is expected to be a reversible process and did not prove to be a complicating factor in practice. Thus, reaction of **10a** in aqueous acetic acid with a combination of ferrous sulfate and sodium nitrite resulted in its clean transformation into alkyne **11a**, which could be isolated in 92% yield.

The remaining isoxazolinones behaved in the same manner giving alkynes **11b−n** efficiently, except for **11h** and **11i**, which were produced in poor yield. This is presumably due to the presence of the ester moiety in a position that causes the ready isomerization of the desired alkynes into highly reactive electrophilic allenes.

We were disappointed, however, to find that exposure of these alkynylamides to the action of a few typical gold-based catalysts did not result in clean or useful transformations. In contrast, reaction of alkynylamide **11a** with *N*-iodosuccinimide (NIS) furnished smoothly iodopyrrolinone **16a** in 72% yield. A plausible mechanism for its formation is outlined in Scheme 3. Thus, electrophilic attack by NIS on the alkyne group to give iodonium species **12a** is followed by closure through the nitrogen of the amide to give cyclic enamide **13a**.[8]

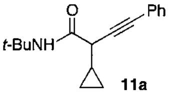
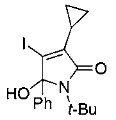
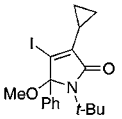
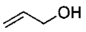
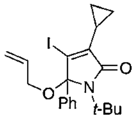
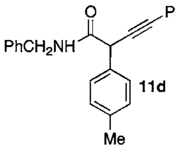
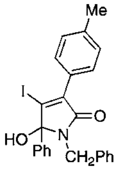
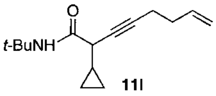
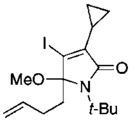
Scheme 3



This compound is nucleophilic enough to undergo a second reaction with NIS leading to intermediate **14a**, which is readily quenched by a nucleophile in the medium, a molecule of water in the present case, to afford diiodo compound **15a**. Finally, elimination of hydrogen iodide generates the observed iodopyrrolinone **16a** in the yield shown.

It is not clear at this moment if the ring-closure proceeding through the nitrogen of the amide is under kinetic or thermodynamic control (or both). Thermodynamic control would imply reversibility of the cyclization step. Iodolaconization of unsaturated amides often leads to lactones rather than lactams[9] and it is interesting to note, in the present context, the observation by Dembinski and co-workers, who found that the reaction of ynones with NIS gave rise to an iodofuran.[10]

Table 2. Formation of Iodopyrrolinones **16**

Alkynylamide 11	Nucleophile (10 equiv)	Pyrrolinone **16**	
	H_2O		**16a** 72%
11a	MeOH		**16b** 76%
11a			**16c** 72%
	H_2O		**16d** 68%
	MeOH		**16e** 70%

This transformation is amenable to a number of variations, both in the structure of the starting alkyne and in the nature of the nucleophile, as indicated by the examples compiled in Table 2. In particular, water may be replaced by an alcohol such as methanol (cf. **16b** and **16e**), or, more interestingly, allylic alcohol (cf. **16c**). In the latter case, it becomes possible

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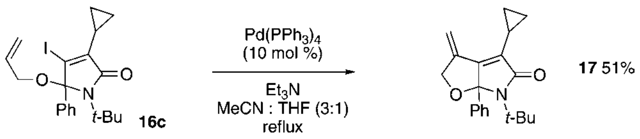
[8] As one referee pointed out, it is possible that that iodination occurs first on the nitrogen of the amide to give the corresponding *N*-iodoamide, which in turn reacts with the alkyne.

[9] (a) Hu, T.; Liu, K.; Shen, M.; Yuan, X.; Tang, Y.; Li, C. *J. Org. Chem.* **2007**, *72*, 8555. (b) Kündig, E. P.; Laxmisha, M. S.; Cannas, R.; Tchertchian, S.; Liu, R. *Helv. Chim. Acta* **2005**, *88*, 1063. (c) Kündig, E. P.; Cannas, R.; Laxmisha, M.; Liu, R.; Tchertchian, S. *J. Am. Chem. Soc.* **2003**, *125*, 5642. (d) Lee, C.-W.; Gil, J. M.; Oh, D. Y. *Heterocycles* **1997**, *45*, 943. (e) Cairns, P. M.; Howes, C.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 627. (f) Takano, S.; Sato, S.; Goto, E.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1986**, 156. (g) Fleet, G. W. J.; Spensley, C. R. C. *Tetrahedron Lett.* **1982**, *23*, 109. For reviews on halocyclizations, see: (h) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2002**, 3099. (i) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681. (j) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 4, p 363. (k) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

[10] (a) Sniady, A.; Wheeler, K. A.; Dembinsky, R. *Org. Lett.* **2005**, *7*, 1769. (b) Rao, M. S.; Esho, N.; Sergeant, C.; Dembinsky, R. *J. Org. Chem.* **2003**, *68*, 6788.

Scheme 4



to apply the Heck reaction to construct a second ring as illustrated by the example displayed in Scheme 4. Indeed, the presence of the vinylic iodide allows the enlisting of numerous transition metal-catalyzed processes to augment considerably the number of possible combinations and opportunities for creating diversity. Access to pyrrolinones by previous methods remains somewhat limited,[11] despite the fact that compounds with related motifs sometimes display interesting biological activities.[12]

In summary, we have now in hand a very practical, efficient, and quite general process for the synthesis of alkynylamides of type **11**. It consists in assembling three components, namely an isoxazolinone, an aldehyde or a ketone, and an isocyanide. Since the first partner is made by reaction of a β-ketoester with hydroxylamine, and therefore very readily accessible, a vast number of combinations are possible. Furthermore, the structural diversity can be augmented by exploiting the efficient NIS induced ring-closure, which incorporates an additional, fourth component, in particular water or an alcohol as shown in Scheme 3 and Table 2, but other nucleophilic reagents may prove suitable.

Acknowledgment. We respectfully dedicate this paper to Prof. Albert Padwa (Emory University). We thank Dr. Hadi Rezaei (Ecole Polytechnique) for preliminary experiments and Ecole Polytechnique for a grant to I.D.-J.

Supporting Information Available: Experimental procedures, full spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902472R

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(11) (a) Howard, E. G.; Lindsey Jr, R. V.; Theobald, C. W. *J. Am. Chem. Soc.* **1959**, *81*, 4355. (b) Ma, S.; Xie, H. *Org. Lett.* **2000**, *2*, 24–3801. (c) Ma, S.; Xie, H. *Tetrahedron* **2005**, *61*, 251. (d) Goh, W. K.; Iskander, G.; Black, D. StC; Kumar, N. *Tetrahedron Lett.* **2007**, *48*, 2287.

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