Tetrahedron Letters 55 (2014) 2150–2153

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of substituted 2,4,5,6-tetrahydrocyclopenta[*c*]pyrazoles and 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazoles by intramolecular nitrilimine cycloaddition

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ARTICLE INFO

Article history:
Received 9 January 2014
Revised 14 February 2014
Accepted 18 February 2014
Available online 28 February 2014

Keywords:
Nitrilimine
Intramolecular 3+2 dipolar cycloaddition
Tetrahydrocyclopentylpyrazoles
Tetrahydropyrrolopyrazoles
N-type Calcium Channel

ABSTRACT

Both substituted 2,4,5,6-tetrahydrocyclopenta[*c*]pyrazoles and 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazoles have been synthesized by the 3+2 intramolecular dipolar cycloaddition of nitrilimines to alkynes. This cyclization has been extended to more versatile 3-bromo derivatives by the use of alkynylbromides as dipolarophiles.

We were interested in synthesizing fused bicyclic pyrazoles **1** where X = C or N[1] as inhibitors of N-type Calcium Channel, a target for neuropathic pain (Fig. 1).[2] One of the most common methods for the synthesis of pyrazoles is the intermolecular condensation of hydrazines with 1,3-dicarbonyl compounds or their derivatives.[3] This approach, though robust, often gives regioisomers such as **2** that require purification with subsequent lower yields. The intramolecular condensation of nitrilimines with tethered alkenes and alkynes to give annulated pyrazoles has gained favor in recent years due to the regiospecificity of the reaction.[4] Also, this reaction has enabled the synthesis of many targets that would be difficult to make by traditional routes. In this Letter, we discuss the synthesis of 2,3-diaryl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazoles **1** (X = C) and 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazoles **1** (X = N) via the intramolecular condensation of nitrilimines with tethered alkynes.

Before our attempts to synthesize **1** using an intramolecular 1,3-dipolar addition reaction, we tried the addition of 2-methoxyphenylhydrazine to 1,3-dione **3** (Scheme 1). Under both basic and acidic conditions, a 2:1 regioisomeric mix of **4** to **5** was the best that we achieved. Attempts to duplicate this synthetic route with intermediates that would give a more robust synthetic handle at the 5-position of the heterocycle, functionality such as ketone or hydroxy, were unsuccessful due to difficulties in accessing these particular 1,3-dicarbonyl intermediates. These issues led us to pursue intramolecular 3+2 cycloadditions to make the desired compounds using a synthesis based on the ring closure of hydrazonyl chlorides **6** and **7** to bicyclic pyrazoles **8** and **9**.

The general scheme for the synthesis of 2,4,5,6-tetrahydrocyclopenta[*c*]pyrazoles **18** is shown below (Scheme 2). Treatment of 4-chlorophenylacetylene **10** with *n*-BuLi/Et_2AlCl followed by addition to the terminal carbon of epoxide **11** gives the addition product **12** in 60% yield as a single regioisomer.[5] Protection of the alcohol with TIPS followed by hydrolysis of the ethyl ester gives the acid **13** in good yield. Formation of the hydrazonyl chloride **15** was accomplished by condensation of the acid **13** with a phenylhydrazine **14** followed by treatment with Ph_3P/CCl_4.[6] The key intramolecular 3+2 dipolar cycloaddition was accomplished

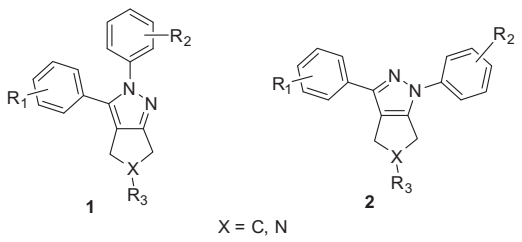

Figure 1. Possible pyrazole regioisomers.

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http://dx.doi.org/10.1016/j.tetlet.2014.02.068
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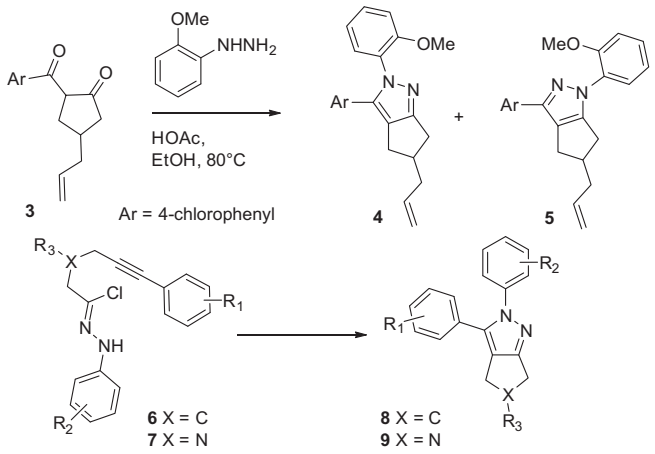
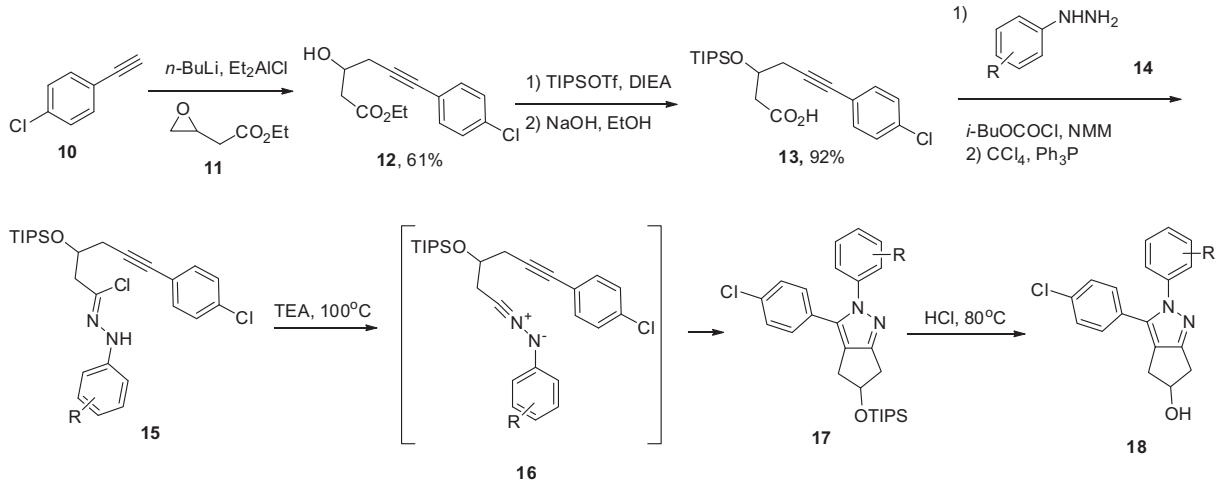


Scheme 1. Comparison of pyrazole syntheses.

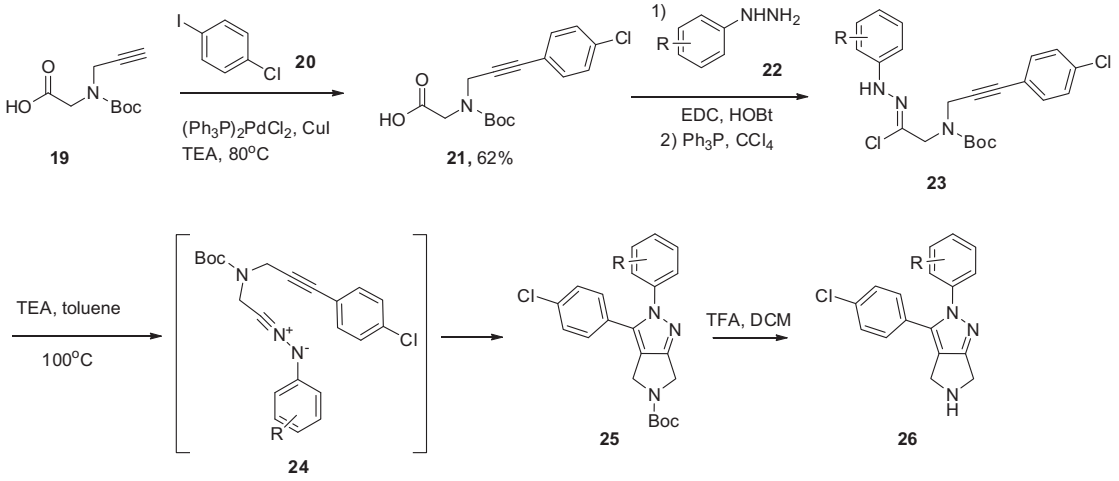
by heating **15** in the presence of triethylamine to generate the intermediate nitrilimine **16**, which reacts in an intramolecular fashion with the tethered alkyne to give the desired 2,4,5,6-tetrahydrocyclopenta[*c*]pyrazole **17** in excellent yield as a single isomer.[7] Deprotection of the TIPS gives the free alcohol **18**, a versatile intermediate for the synthesis of many N-type Calcium Channel inhibitors. It should be noted that the use of commercially available (*R*)- or (*S*)-**10** in the reaction sequence gives the chiral 5-hydroxycyclopentylpyrazole.

After the success we had in making the cyclopentylpyrazoles, we applied similar chemistry to the synthesis of 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazoles **26** (Scheme 3). Treatment of alkyne **19** with **20** under Sonagashira conditions gives **21**. Coupling of **21** with aryl hydrazines **22** gives the hydrazide, which can be converted to the hydrazonyl chloride **23** by treatment with Ph_3P/CCl_4. Heating **23** to 100 °C in the presence of triethylamine generates the 1,3-dipolar intermediate **24** which reacts with the alkyne to give the desired 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole **25** as a single regioisomer in excellent yield.[8] Deprotection of the Boc furnishes versatile intermediate **26**.

Comparative yields for various R groups on the arylhydrazine are shown (Tables 1 and 2). Overall, purified yields for the intramolecular 1,3-dipolar cycloaddition reaction were very good, most above 80%. A few exceptions were noted for 2-dimethylamino **43**, 2-nitro **44**, and 2,3-methylenedioxy **45** in the formation of the pyrrolopyrazoles. For the cyclopentylpyrazoles, it is worth noting that 2-methoxy **28** consistently gave yields in the 70% range in toluene, but switching to dioxane gave an increase to 96%. When using phenylhydrazine in both syntheses, the intermediate hydrazonyl



Scheme 2. Synthesis of 2,4,5,6-tetrahydrocyclopenta[*c*]pyrazoles.



Scheme 3. Synthesis of 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazoles.

Table 1
Comparative yields for the nitrilimine cyclization to form 2,4,5,6-tetrahydrocyclopenta[*c*]pyrazoles **17** and **18**

Compd no.	R	Solvent	Yield[a] (%)
27	2-OCF_3	Toluene	69
28	2-OMe	Toluene	64–72
28	2-OMe	Dioxane	96
29	2-OEt	Toluene	85
30	2-OMe-4-Cl	Dioxane	95
31	2,3-Dihydrofuran	Dioxane	93
32	H		37[b]

[a] Yield includes deprotection of TIPS by heating with 1 N HCl in dioxane.
[b] Cyclization occurred during the Ph_3P/CCl_4 step.

Table 2
Comparative yields for the nitrilimine cyclization to form 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazoles **25** and **26**

Compd no.	R	Yield (%)
33	2-Ethyl	91
34	2-CF_3	90
35	2-OCF_3	92
36	2-OMe	84
37	2-OEt	98[a]
38	2-Me-4-OMe	90
39	2-OMe-4-F	85
40	2-OMe-4-Me	93
41	2-F-4-OMe	95
42	2-OMe-4-Cl	99
43	2-NMe_2	58
44	2-NO_2	71
45	2,3-Methylenedioxy	59[a]
46	2,3-Dihydrofuran	91[a]
47	H	17[b]

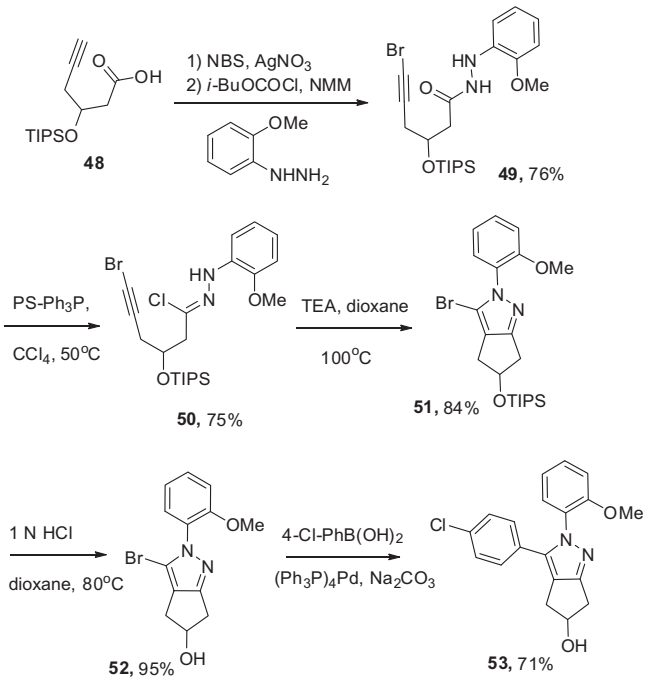
[a] Yield includes deprotection of the Boc by treatment with TFA/DCM.
[b] Cyclization occurred during the Ph_3P/CCl_4 step.

chloride could not be isolated from the Ph_3P/CCl_4 reactions, and instead the cyclized cyclopentylpyrazole **32** and pyrrolopyrazole **47** products were isolated directly from the reaction mixture.[9]

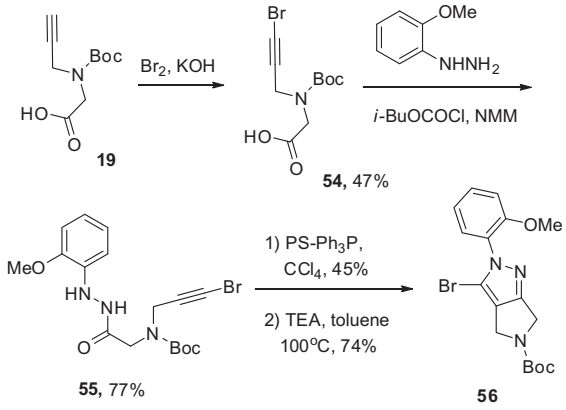
One limitation of this chemistry was the necessity to carry the aryl group on the alkyne through many synthetic steps. To enable the synthesis of analogs at the 3-position of the pyrazole later in the synthesis, 3-bromo-cyclopentylpyrazole **51** was targeted (Scheme 4). The 3+2 dipolar cycloaddition of a nitrilimine with an alkynylbromide to form a bromopyrazole is unprecedented, either by intra- or intermolecular reaction. Treatment of **48** with NBS and silver nitrate followed by coupling with 2-methoxyphenyl hydrazine gives bromohydrazide **49**.[10] Reaction of **49** with Ph_3P/CCl_4 gives a low yield due to loss of bromine from the alkyne. Attempts to remedy this by changing solvent, amounts of reagents, and surveying other reaction conditions were initially unsuccessful. However, substitution of Ph_3P with polymer-bound Ph_3P and heating to 50 °C in acetonitrile gives the desired hydrazonyl chloride **50** in 75% yield. Cyclization using TEA in dioxane at 100 °C gives the 2-aryl-3-bromocyclopentylpyrazole **51** in 98% yield, an important intermediate for the synthesis of diverse N-type inhibitors **53** via palladium coupling reactions.

For the pyrrolopyrazole series, treatment of the alkyne **19** with bromine and KOH gives the bromoalkyne **54** (Scheme 5).[11] Following the same general synthetic scheme described previously gives the desired 3-bromopyrrolopyrazole **56** in 45% yield for the chlorination and 74% yield for the intramolecular 1,3-dipolar cycloaddition reaction.

We have shown that the intramolecular 3+2 dipolar cycloaddition of nitrilimines to tethered alkynes is a versatile way to synthesize a variety of substituted 2,3-diaryl-cyclopentyl- and pyrrolopyrazole derivatives. The ease of synthesis of intermediates



Scheme 4. Synthesis of 3-bromocyclopentylpyrazole **51**.



Scheme 5. Synthesis of 3-bromopyrrolopyrazole **56**.

for the dipolar cycloaddition reaction, and the formation of a single regioisomer in that reaction, are considerable improvements on the traditional ways to synthesize pyrazole derivatives. We have also extended the chemistry to include alkynylbromides as the dipolarophile giving the versatile 2-aryl-3-bromo derivatives that enable the synthesis of a variety of analogs at the 3-position of the pyrazole. Lastly, we have shown that PS-Ph_3P can be an important reagent to use in the Wolkoff reaction to generate sensitive hydrazonyl chlorides.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.068. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Aubert, T.; Tabyaoui, B.; Farnier, M.; Guilard, R. *Synthesis* **1988**, 742.

2. Yamamoto, T.; Takahara, A. *Curr. Top. Med. Chem.* **2009**, *9*, 377.
3. (a) Fustero, S.; Simon-Fuentes, A.; Sanz-Cerveram, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253; (b) Yoon, J.-Y.; Lee, S.; Shin, H. *Curr. Org. Chem.* **2011**, *15*, 657; (c) Makino, K.; Kin, H. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1998**, *35*, 489; (d) Kumar, S.; Yadav, S.; Raghava, B.; Saraiah, B.; Ila, H.; Rangappa, K.; Hazra, A. *J. Org. Chem.* **2013**, *78*, 4960.
4. Broggini, G.; Molteni, G.; Zecchi, G. *Heterocycles* **1998**, *47*, 541.
5. Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028.
6. Wolkoff, P. *Can. J. Chem.* **1975**, *53*, 1333.
7. Padwa, A.; Nahm, S.; Sato, E. *J. Org. Chem.* **1978**, *43*, 1664.
8. Molteni, G. *Heterocycles* **2004**, *63*, 1423.
9. These were single reactions and are unoptimized. Perhaps the electron-donating effects of the substituents commonly used (necessary for N-type calcium channel activity) destabilize the nitrilimine intermediate, while neutral phenyl stabilizes it and thus encourages the cyclization at rt. Or perhaps the *ortho*-substituent twists the aryl out of plane from the nitrilimine destabilizing it, while the phenyl remains in the plane and stabilizes the nitrilimine by delocalizing the charge.
10. Leroy, J. *Synth. Commun.* **1992**, *22*, 567.
11. Brandsma, L.; Verkruijsse, H. D. *Synthesis* **1990**, *11*, 984.