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Synthesis of triazole-functionalized tetrahydroindazolones by 1,3-dipolar cycloadditions between azides and alkynes

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ABSTRACT

7-Azido-tetrahydroindazolones undergo efficient copper-catalyzed Huisgen 1,3-dipolar cycloaddition reactions with various alkynes leading to a straightforward synthesis of triazole-functionalized tetrahydroindazolones. The latter are interesting molecular platforms in terms of medicinal chemistry.

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Tetrahydroindazoles (THIs), as a subclass of fused-pyrazoles, have gained significant interest due to the broad spectrum of their biological activity. Thus, 2-aryl derivatives of 4,5,6,7-THI have been reported to be active as herbicides[1] whilst their 5-carboxylic acid derivatives possess anti-inflammatory properties.[2] Additionally, 5-amino-4,5,6,7-tetrahydroindazoles possess dopaminergic activity[3] and THI-substituted 3,5-dihydroxy-6-heptenoic acids have shown HMG-CoA reductase inhibiting activity with IC_{50} = 3.0 nM.[4]

Tetrahydroindazolones of general structure **1a** possess antitumor activity while being less toxic than other available antitumor drugs (Fig. 1).[5] These derivatives have also shown other valuable biological activities connected with cell proliferative disorders, and in the treatment of Alzheimer's disease. On the other hand, compounds **1b** are known for their selectivity toward GABA-A α 5 receptors and are useful for enhancing cognition.[6] More recently, other THI-3-carboxamides have been found to regulate the mitotic motor protein, Eg5.[7] Specific inhibition of the latter prevents uncontrollable division of malignant cells. Furthermore, THIs **1c** were shown to be active against various carcinomas.[8] Compounds with the general formula **1d** are potent inhibitors of Heat-Shock Protein 90.[9]

Additionally, scaffolds similar to **1** have raised a theoretical interest as privileged molecular platforms for the synthesis of selective cyclooxygenase-2 inhibitors[10] and searches in the THI series have led to the discovery of inhibitors of bacterial type II topoisomerases.[11] The corresponding 4-deoxy-analogs of **1** have been studied as thrombin inhibitors where THI acts as a heterobicyclic P_1-arginine side-chain mimetic.[12] Additionally, tetrahydroindazolones have been used as intermediates for the synthesis of selective and drug-like ligands for the opioid σ1 receptor.[13]

In the light of these facts, structural[14] and synthetic interest in the field of differently substituted 4,5,6,7-THIs has continued.[15] Various 2-(2,6-dichloro-4-trifluoromethyl-phenyl)tetrahydroindazoles[16] and tetrahydroindazol-3-yl alanine derivatives,[17] as well as novel THI-based chiral auxiliaries,[18] have been reported in the last decade. Modern technologies have also been used in THI syntheses. For example, reactions under microwave irradiation have been reported.[19] Claramunt, Lopez, and co-workers[20a] studied the synthesis and particularly the tautomeric equilibrium of tetrahydroindazolones related to those reported by us earlier[20b].

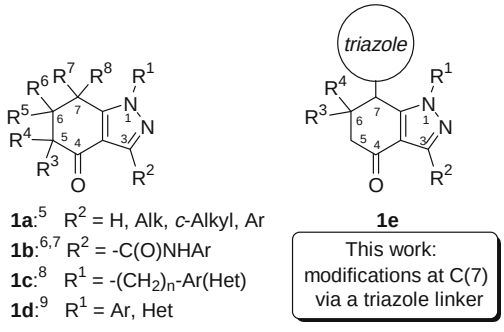

Figure 1. Generalized scaffolds of tetrahydroindazolones.

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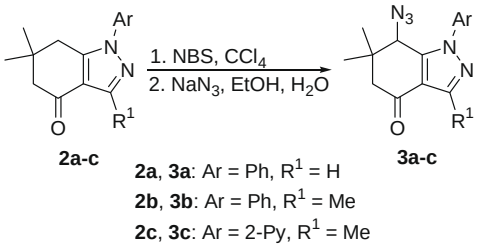


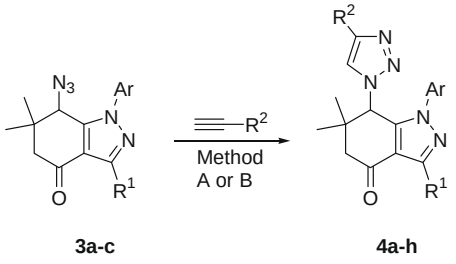
Scheme 1. Synthesis of **7**-azido THIs.

However, to the best of our knowledge, there are no reports describing heterocyclic substituents/linkers at C(7) of the pharmacologically privileged structure **1**. Hence, we decided to explore the synthesis of C(7)-triazole derivatives of 1-aryl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazoles (**1e**). The latter correspond to the general molecular platform **1** depicted in Figure 1.

Since the discovery of efficient catalysis of the Huisgen dipolar cycloadditions between alkynes and azides,[21] this reaction has become important in the field of derivatization of different molecular scaffolds. Moreover, triazoles themselves possess interesting biological activities.[22]

Thus, bromination of THIs **2a–c** with N-bromosuccinimide (NBS) in refluxing carbon tetrachloride followed by treatment with NaN_3 led to azides **3a–c** as reported earlier (Scheme 1).[23] We investigated two methods for the copper-catalyzed 1,3-dipolar cycloaddition reaction. Method A utilizes the $CuSO_4{\cdot}5H_2O$–Cu couple in *tert*-butanol/water[24] and method B uses $CuSO_4{\cdot}5H_2O$ with sodium ascorbate in acetone/water.[21a,25] The results are summarized in Scheme 2 and Table 1.

Reaction of azide **3a** and phenylacetylene according to method A at 80 °C for eight hours provided phenyltriazole-functionalized THI **4a** in 85% yield. On the other hand, method B afforded **4a** in 72% yield after 24 h at 20 °C. In general, higher temperatures and longer reaction times gave better yields. 1-Phenyl/pyridyl-7-([1,2,3]triazol-1-yl)-4,5,6,7-tetrahydroindazol-4-ones **4a–h** containing phenyl, hydroxymethyl, hydroxypropyl, formyl, and ethoxycarbonyl functions at C(4′) were obtained in good to excellent yields.

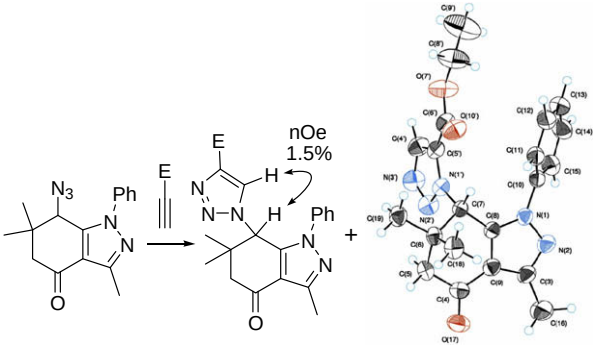


Scheme 2. Synthesis of triazole-functionalized tetrahydroindazolones **4a–h**.

Triazoles with $R^2 = CH_2OH$ (**4b**, **4f**), $R^2 = COOEt$ (**4c**), $R^2 = (CH_2)_3OH$ (**4e**), and $R^2 = CHO$ (**4h**) are suitably functionalized for further transformation.

Reactions with ethyl propiolate were sluggish, gave mediocre yields and often mixtures of regioisomers. The only exception was starting material **3a**, which provided product **4c** in 70% isolated yield. On the other hand, pyridyl derivative **3c** gave inseparable mixtures of products. Interesting results were obtained with tetrahydroindazolone **3b**. Thus, method A (80 °C, 22 h) gave full conversion to triazoles **4i** and **4j** in a ratio of 74:26 and an isolated yield of 91% (Scheme 3). In contrast, catalytic conditions at lower temperature or thermal conditions furnished both regioisomers in almost a 1:1 ratio. The structure of **4j** was established unambiguously by single crystal X-ray diffraction.[26] The structure of regioisomer **4i** was confirmed from the $^1H\{^1H\}$ nuclear Overhauser effect between H–C(7) and H–C(5′) which was established to be relatively small (1.5%). Triazole-functionalized THI **4c** gave a respective NOE of 2.3%.

As expected, dimethyl acetylenedicarboxylate underwent the Huisgen cycloaddition under thermal conditions (Scheme 4). Tetrahydroindazole-substituted 1H-[1,2,3]triazole-4,5-dicarboxylic acid dimethyl esters **4k** and **4l** were obtained in 59% and 40% isolated yields, respectively.



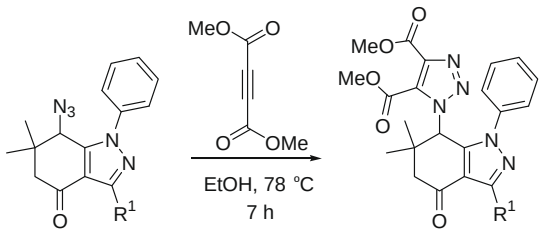
a) Method A (80 °C, 22 h); b) EtOH, reflux, 22 h;
c) Method A (60 °C, 21 h)

Scheme 3. Regioselectivity in the 1,3-dipolar cycloaddition of azide **3b** and ethyl propiolate.

Table 1
Triazole-functionalized tetrahydroindazolones **4a–i** produced via methods A or B

Entry	Product **4**	R^1	Ar	R^2	Method	Yield (%)	Mp (°C)
1	**4a**	H	Ph	Ph	A[a] (80 °C, 8 h)	85	172–173
2	**4a**	H	Ph	Ph	B[b] (20 °C, 24 h)	72	175–176
3	**4b**	H	Ph	CH_2OH	A (30 °C, 48 h)	60	189–190
4	**4c**	H	Ph	COOEt	A (80 °C, 11 h)	70	180–181
5	**4d**	Me	Ph	Ph	A (80 °C, 16 h)	87	148–149
6	**4e**	Me	Ph	$(CH_2)_3OH$	A (80 °C, 5 h)	89	52–55
7	**4f**	Me	2-Py	CH_2OH	A (80 °C, 27 h)	89	215–216
8	**4g**	Me	2-Py	Ph	A (80 °C, 12 h)	98	189–190
9	**4h**	Me	2-Py	CHO[c]	A (80 °C, 30 h)	53	183–185

[a] $CuSO_4{\cdot}5H_2O$, Cu, *t*-BuOH, H_2O.
[b] $CuSO_4{\cdot}5H_2O$, sodium ascorbate, acetone, H_2O.
[c] The corresponding diethylacetal ($R^2 = CH(OEt)_2$) was employed as the reagent.

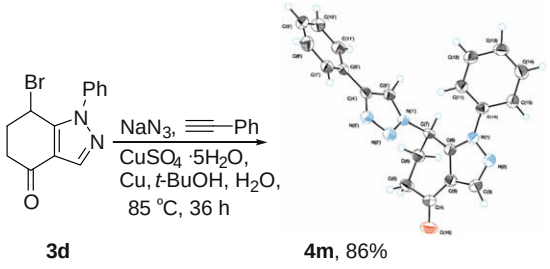


Scheme 4. Thermal 1,3-dipolar cycloaddition of 7-azido-THIs **3a**,**b** with dimethyl acetylenedicarboxylate.

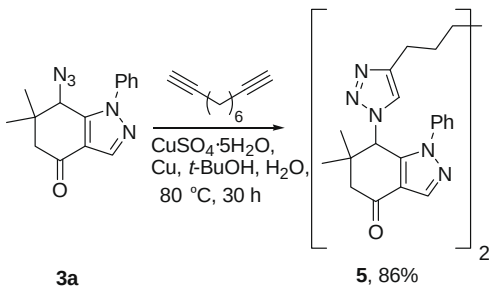
Next, we turned our attention to 7-bromo-1-phenyl-4,5,6,7-tetrahydroindazol-4-one **3d** (Scheme 5). This substrate formed elimination and aromatization products when treated with sodium azide under standard conditions. As a consequence, we were unable to isolate the required azide. However, a one-pot procedure which involved heating bromide **3d**, NaN_3, and phenylacetylene in the presence of the copper-couple according to method A provided the expected triazole **4m** in 86% yield.[27]

The spectroscopic and physical properties (^{1}H NMR and mass spectra, and/or CHN analysis) of all new compounds were fully consistent with the assigned structures.[28] The chemical shifts of H–C(7) depend on both the N(1) substituents of the THIs, and C(4,5) of the triazole. The presence of a methoxycarbonyl group at the latter position shifts H–C(7) upfield (6.13 ppm relative to TMS). On the contrary, the presence of the N(1)-pyridyl group results in a downfield shift (6.70 ppm relative to TMS). On the other hand, both H–C(5) show a typical AB system with $^2J \approx 17$ Hz.

Our further research is connected with the synthesis and biological activity evaluation of THI oligomers and conjugates with natural scaffolds. To this end, we have pursued initial dimerization experiments of THIs via extended bis-triazole-linkers. Thus, THI-azide **3a** underwent double 1,3-dipolar cycloaddition to provide a diastereomeric mixture of dimer **5** in 86% yield (Scheme 6).



Scheme 5. One-pot synthesis of triazole-functionalized tetrahydroindazolone **4m**.



Scheme 6. Synthesis of a THI dimer with an extended bis-triazole-linker.

In conclusion, we have developed a straightforward synthesis of triazole-functionalized tetrahydroindazolones that are interesting molecular platforms in terms of medicinal chemistry. In order to use these structures for conjugation with compounds from natural sources (carbohydrates, peptides, etc.) and/or oligomerization, homochiral forms of the corresponding azido-THIs **3a–c** are required. Studies toward this end are underway in our laboratory and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.009.

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26. Crystallographic data for **4j** have been deposited with the Cambridge Crystallographic Data Centre as a Supplementary Publication No. CCDC 719565.
27. Crystallographic data for **4m** have been deposited with the Cambridge Crystallographic Data Centre as a Supplementary Publication No. CCDC 719566.
28. For experimental procedures and characterization of products, see Supplementary data.