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Sulur G Manjunatha, Sreekanth Bachu, Vasantha Krishna Kadambar, Andiappan Murugan, Sridharan Ramasubramanian, Puranik Ramachandra, Sudhir Nambiar

PII: S0040-4039(14)00670-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.04.058
Reference: TETL 44520

To appear in: *Tetrahedron Letters*

Received Date: 13 March 2014
Revised Date: 11 April 2014
Accepted Date: 15 April 2014

Please cite this article as: Manjunatha, S.G., Bachu, S., Kadambar, V.K., Murugan, A., Ramasubramanian, S., Ramachandra, P., Nambiar, S., A novel synthetic approach to 4-acetamido-1-arylindazoles via Semmler-Wolff rearrangement of 1-aryl-6,7-dihydro-5H-indazol-4-one oxime, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.04.058

Graphical Abstract

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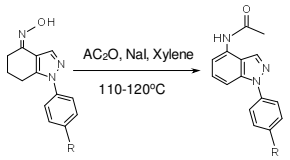

Tetrahedron Letters
journal homepage: www.elsevier.com

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AstraZeneca India Pvt. Ltd, Off Bellary Road, Bangalore – 560024, India.

ARTICLE INFO

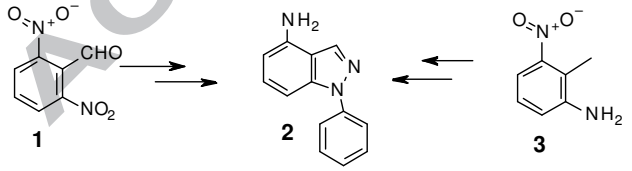
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
4-acetamido-1-phenylindazole
Dihydroindazol-4-one
Semmler-Wolff aromatization
Acetic anhydride
Sodium Iodide

ABSTRACT

A simple and efficient procedure for the syntheses of 4-acetamido-1-arylindazoles from corresponding 1-aryl-6,7-dihydro-5H-indazol-4-one oximes by Semmler-Wolff aromatization using acetic anhydride and sodium iodide is reported.

Indazoles are key building blocks to many pharmaceutically important molecules having wide range of biological activities.[1] Recently 4-substituted aminoindazole derivatives have been shown to exhibit herbicidal, anti-infective and anti–inflammatory properties.[2] In literature many synthetic procedures are reported for the preparation of indazoles but very few methods are described for the synthesis 4-aminoindazoles. Generally, these are prepared by the reaction of 2,6-dinitrobenzaldehyde with phenyl hydrazine followed by reduction of nitro group.[3] Another approach followed for 4-aminoindazole is the diazotization of 2-methyl-3-nitroaniline to get 4-nitroindazole followed by the reduction of the nitro group and further derivatised to get the amino derivative.[4]



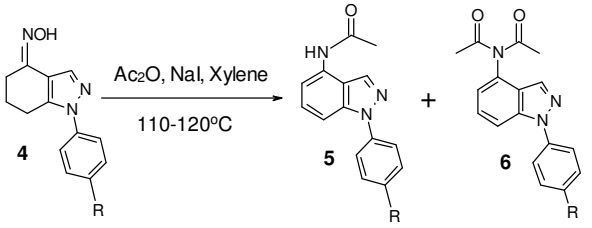
Scheme 1

The major limitations of the above synthetic methods are that that these require 1,2,3-suitably substituted aromatic compounds such as **1** and **3**, as the starting materials. Moreover, these procedures involve energetic intermediates and starting materials which may pose significant challenge for the scale up. Recently, a few notable methods are reported for the syntheses of 4-aminoindazoles via Buchwald amination of 4-haloindazoles.[5] We believe that there is a need for the development of practical and safe alternative synthetic route to 4-aminoindazoles. We envisaged that Semmler-Wolff aromatization protocol would provide an efficient route to the synthesis of 4-acetamidoindazoles.

Semmler-Wolff rearrangement, described by Semmler[6] and later developed by Wolff[7], is the aromatization of cyclohexenone oximes to corresponding anilines by a variety of acidic reagents.[8] The advantage of this reaction is that it places the amine function on the ring system in a very simple way which otherwise difficult to introduce by any standard methods. Semmler-Wolff aromatization has been utilized for the synthesis of benzenoid rings, fused heterocyclic systems and have been well reported in literature.[9] Generally, this transformation is performed in strong acidic medium or in a mixture of acetic anhydride and an acid like acetic acid, hydrogen chloride, phosphoric acid, sulfuric acid or methanesulfonic acid. These protocols suffer low yield due to the competing Beckmann rearrangement. Recently while exploring a safe and scalable manufacturing process for a 4-aminoindole derivative, we have developed an efficient process for this transformation which involves sodium iodide and acetic anhydride as reagents and xylene as solvent. This process was clean and offered better selectivity towards Semmler-Wolff rearrangement. We have demonstrated the efficiency of this process in the large scale synthesis of

* Corresponding author. Tel.: +91 80 6621300, Extn No: 7260; fax: +91-80-23622011; e-mail: Manjunath.Sulur@astrazeneca.com

AZD1981.[10] We ought to explore the application this protocol in the syntheses of many other fused carbocylic and heterocyclic compounds with amine function at a specific position. Herein, we report a practical synthesis of 1-aryl-4-acetamidoindazoles **5** using our process starting from 1,3-cyclohexanedione as shown in Schemes 2 and 3.



Scheme 2

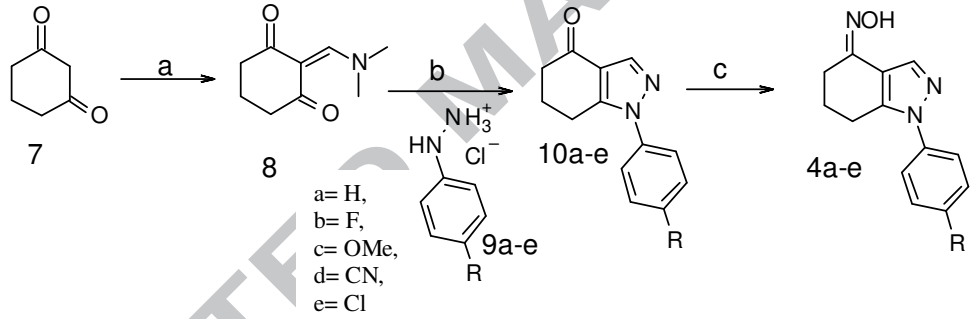
The synthesis of 1-aryl-6,7-dihydro-5H-indazol-4-one oxime (**4**) began by reflxing 1,3-cyclohexanedione (**7**) with *N,N*-dimethylformamide diisopropylacetal in toluene to form the vinylogous enamide **8** in 87% yield. The enamide **8** was subjected to cyclization with the aryl hydrazines **9** to form the keto intermediate **10**. The keto intermediate **10** was converted into corresponding oximes **4** by standard process.[11,12] The results are tabulated in Table 1. Practically, the keto intermediate **10** required no isolation and could be converted to the oxime in one pot[13].

Semmler-Wolff aromatization of 1-phenyl-6,7-dihydro-5H-indazol-4-one oxime (4a):

As planned, the oxime compound **4a** was heated in a mixture of acetic anhydride and xylene in the presence of catalytic amounts of sodium iodide at 110-120 °C for about 2 h. The progress of the reaction was monitored by HPLC/LCMS. The reaction progressed smoothly to get the required 4-acetamido-1-phenylindazole and no Beckmann products were observed. However formation of the *N,N*-diacetyl impurity **6** (5-10%) was observed under these conditions, which disintegrated in to the required product during the base work-up. The desired indazole **5a** was then isolated in good yield by basification and aqueous work-up followed by a simple column chromatography.[13]

The generality of this reaction was studied with a variety of other oximes (**4b-e**) prepared in a similar way using substituted phenylhydrazines and the results are tabulated in Table 2.

As shown in Table 2, a wide range of oximes underwent Semmler-Wolff aromatization to afford the desired products in good yield. In general, this Semmler-Wolff aromatization reaction condition worked well with both electron rich and poor aryl systems. Further studies on Semmler-Wolff aromatization using aryl and hetero-aryl phenylhydrazines with substituents at various positions were also very successful yielding indazoles in good yield and are tabulated in Table 3.



Reaction conditions: (a) Toluene, dimethylfomamide diisopropyl acetal, reflux for 2h. (b) Aq.HCl, IPA, water, 65-70°C, 1-2 h (c) $NH_2OH.HCl$, NaOAc, Water, IPA, 65-70 °C, 2 h

Scheme 3

Table 1: Examples of ketone and oxime intermediates

S.No	R	Product	Yield (%)	Product	Yield (%)
1	H	**10a**	94	**4a**	94
2	F	**10b**	90	**4b**	90
3	OCH_3	**10c**	85	**4c**	85
4	CN	**10d**	90	**4d**	90
5	Cl	**10e**	90	**4e**	90

Table 1

Table 2: Examples of Semmeler-Wolff aromatization

S.No	R	Substrate	Product	Reaction Time (h).	Yield in (%)
1	H	**4a**	**5a**	2.0	80
2	F	**4b**	**5b**	2.5	75
3	OCH_3	**4c**	**5c**	4.5	78
4	CN	**4d**	**5d**	2.5	72
5	Cl	**4e**	**5e**	2.5	75

Table 2

Table 3 Semmler-Wolff aromatization of aryl and hetero-aryl substrates

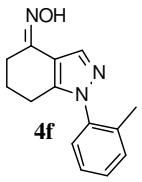
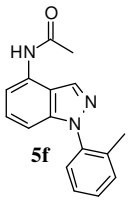
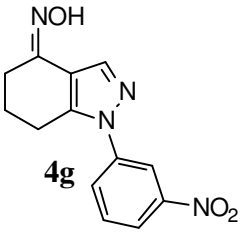
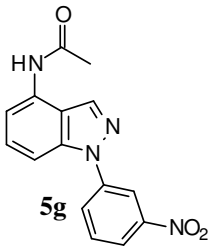
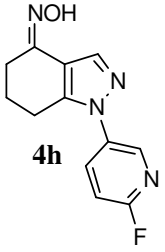
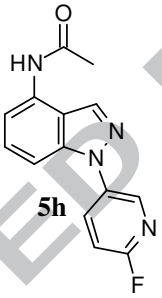
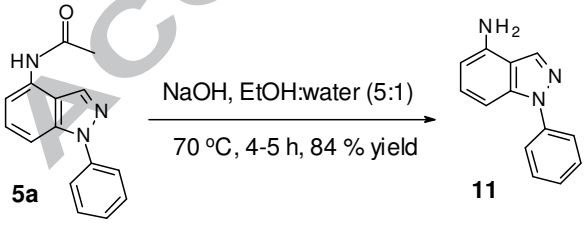
S.No	Substrate	Product	Time	Yield
1	 **4f**	 **5f**	3	72
2	 **4g**	 **5g**	2.5	75
3	 **4h**	 **5h**	3	72

Table 3

The product 4-acetamido-1-arylindazoles **5** could be hydrolyzed by heating with sodium hydroxide in ethanol to 4-amino-1-arylindazoles **11** as shown in Scheme 4.



Scheme 4

In summary, we have described a simple and efficient sodium iodide catalyzed Semmler-Wolff aromatization method for the preparation of 4-acetamido-1-arylindazoles from 1-aryl-6,7-dihydro-5H-indazol-4-one oximes. The method appears to be general and works well with both aryl and heteroaryl substituted oximes.

Acknowledgements:

The authors are thankful to management team of AstraZeneca for their timely support. We also thank Jayan Rapai for analytical support and Bill Moss for helpful comments.

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13. Representative Procedures

Synthesis of TetrahydoIndazole-4-one (10a): To a stirred solution of 2-dimethylaminomethylenecyclohexane-1,3-dione **8** (2.5g, 14.95 mmol) in isopropanol (37.5 mL) and water (5.0 mL) mixture was added phenylhydrazine hydrochloride **9a** (2.38g, 16.44 mmol) and catalytic amount of concentrated hydrochloric acid (0.054g,1.495 mmol) at 20-25 ºC. The resultant mixture was allowed to warm to 65-70 ºC and stirred for 1.0-2.0 h, by which time the reaction was completed as indicated by TLC. The reaction mixture was then quenched with excess of water (37.5 mL) and stirred for 2.0 h. The product was filtered and dried in oven at 50 ^{o}C.

1-phenyl-6,7-dihydro-5H-indazol-4-one oxime (4a): To a stirred solution of tetrahydoindazole-4-one **10a** (1.5g, 7.06 mmol) in isopropanol (22.5 mL) and water (3.0 mL) mixture, was added hydroxylamine hydrochloride (0.54g, 7.77 mmol) and sodium acetate (0.69g, 8.48 mmol) at 20-25ºC. The resultant mixture was warmed to 65-70 ºC and stirred for 0.5-1.0 h, by which time the reaction was completed as indicated by LCMS. The reaction mixture was then quenched with water (22.5 mL) and stirred for additional 2.0 h. The precipitated product was then filtered and dried in oven at 50 ^{o}C.

One-pot synthesis; 1-phenyl-6,7-dihydro-5H-indazol-4-one oxime (4a):

To a stirred solution of 2-dimethylaminomethylene cyclohexane-1,3-dione **8** (2.5g, 14.95 mmol) in isopropanol (37.5 mL) and water (5.0 mL) was added phenylhydrazine hydrochloride **9a** (2.38g, 16.44 mmol) and catalytic amount of concentrated hydrochloric acid (0.054g,1.495 mmol) at 20-25 ºC. The resultant mixture was stirred at 65-70 ºC for 1.0-2.0 h, by which time the reaction was completed as indicated by TLC. The reaction mass was cooled to 20-25 ºC followed by the addition of hydroxylamine hydrochloride (1.14g, 16.44 mmol) and sodium acetate (1.47g, 17.94 mmol). The resultant mixture was heated to 65-70 ºC and stirred for 0.5-1.0 h, by which time the reaction was completed as indicated by LCMS. The reaction mixture was cooled to 20-25 ºC, quenched with water (22.5 mL) and stirred for additional 2.0 h. The precipitated product was filtered and dried in oven at 50 ^{o}C.

4-Acetamido-1-phenyl indazol (5a): To a stirred solution of 1-phenyl-6,7-dihydro-5H-indazol-4-one oxime **4a** (1.5g, 6.06 mmol) in acetic anhydride (4.5mL) and xylene (15.0 mL) mixture was added sodium iodide (0.49g, 3.30 mmol) at 20-25 ºC. The resultant mixture was heated to 110-120 ºC and stirred for 2.0 h, by which time the reaction was completed as indicated by TLC. The reaction mixture was cooled to 20-25 ^{o}C then concentrated under vacuum. The residue was treated with 1M aqueous sodium hydroxide solution (5 mL) and extracted with dichloromethane (2X50 mL). The organic layer was washed with water (2X20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product **5a**. The crude product was then purified by column chromatography on silica gel (hexane/ethyl acetate, 2:8) to obtain the pure product as yellow solid.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at