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PII: S0040-4039(18)30795-0
DOI: https://doi.org/10.1016/j.tetlet.2018.06.041
Reference: TETL 50079

To appear in: *Tetrahedron Letters*

Received Date: 27 April 2018
Revised Date: 8 June 2018
Accepted Date: 15 June 2018

Please cite this article as: Davies, R.D.M., Pink, J.H., Scott, J.S., Bailey, A., Synthesis of 8-substituted-6-phenyl-6,7,8,9-tetrahydro-3*H*-pyrazolo[4,3-*f*]isoquinolines using Pictet-Spengler and Bischler-Napieralski cyclisation methods, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.06.041

Tetrahedron Letters
journal homepage: www.elsevier.com

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Robert D.M. Davies, Jennifer H. Pink, James S. Scott, Andrew Bailey*

Medicinal Chemistry, Oncology, IMED Biotech Unit, AstraZeneca, Macclesfield SK10 4TG, United Kingdom

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
6,7,8,9-tetrahydro-3*H*-pyrazolo[4,3-*f*]isoquinoline
Pictet-Spengler
Bischler-Napieralski

ABSTRACT

In the following communication we report routes for the synthesis of a set of 8-substituted-6-phenyl-6,7,8,9-tetrahydro-3*H*-pyrazolo[4,3-*f*]isoquinolines. Pictet-Spengler and Bischler-Napieralski methodologies were employed on the relevant indazole precursors and the merits of the two cyclisation reactions for preparing these structures were assessed.

Hydroxy-substituted tetrahydroisoquinolines have been explored as potential ligands in a variety of therapeutic areas, such as dopamine antagonists, nitric oxide inhibitors, opioid K antagonists and phenylethanolamine *N*-methyltransferase (PNMT) inhibitors.[1a-d] However, the phenolic hydroxy group has been associated with *in vivo* liabilities in many different molecules investigated as oral drugs. To overcome these issues, several reports have demonstrated the use of indazole as a potential isostere of phenol which can offer benefits in terms of pharmacokinetic profile.[2a-c] During a recent drug discovery project we wished to investigate this in the context of a 6-hydroxytetrahydroisoquinoline scaffold and synthesize an analogous series with the isosteric tricyclic indazole cores **1a-c** (Fig. 1). Traditional approaches to the tetrahydroisoquinoline scaffold often utilise a Pictet-Spengler or Bischler-Napieralski cyclisation to construct the piperidine ring.[3] Substituted, electron-rich phenols are well suited to this chemistry, however less electron rich aromatic systems perform poorly, or not at all, in the cyclisation step and literature precedent for electron poor indazole rings participating in these cyclisations was notably absent. Our first-generation route to these targets therefore involved construction of the tetrahydroisoquinoline 'core' followed by elaboration of an *o*-toluidine functionality to the appropriate indazole (Scheme 1).

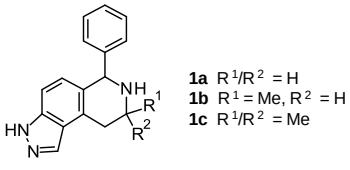
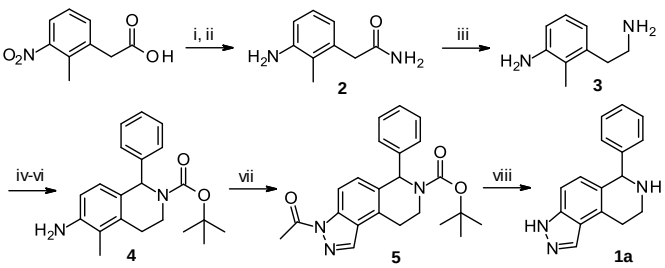


Figure 1. Target tricyclic indazoles **1a-c**



Scheme 1. Reagents and conditions: (i) NH_4Cl, HATU, DIPEA, CH_2Cl_2, rt, 100%; (ii) H_2, Pd/C, methanol, rt, 97%; (iii) $BH_3{\cdot}Me_2S$, THF, reflux, 64%; (iv) benzaldehyde, aq. phosphate buffer/MeCN, 50 °C; (v) TFA, 90 °C, 44% (2 steps); (vi) Boc_2O, Et_3N, aq. dioxane, rt, 75%; (vii) KOAc, Ac_2O, Toluene/$CHCl_3$, 60 °C, then 18-Crown-6, isoamylnitrite, 60 °C, 43%; (viii) HCl, dioxane/MeOH, rt, 95%.

The *o*-toluidine intermediate **4** was formed in 6 steps from commercially available 2-methyl-3-nitrophenylacetic acid. An initial coupling using ammonium chloride as a source of ammonia followed by catalytic hydrogenation of the nitro group both proceeded in good yield, leading to amide **2**. Reduction with borane dimethylsulfide gave the phenethylamine **3** which was then reacted with benzaldehyde in a Pictet-Spengler cyclisation followed by Boc protection to yield intermediate **4**. It is worth noting that the Pictet-Spengler cyclisation of phenethylamines in which the aryl ring is substituted by 'NH_2' has poor literature precedent. The method we followed (based on a report by Hailes and co-workers[4]) allowed isolation of the intermediate imine which was further elaborated into the desired tetrahydroisoquinoline by heating in TFA. A modified Jacobsen procedure involving 18-crown-6 as a phase transfer reagent was

then used to take the *o*-toluidine functionality in **4** through to the acyl protected indazole **5** in 43% yield.[5] The synthesis was completed by removal of the Boc and acyl protecting groups under acidic conditions and target **1a** was thus isolated in 8 steps in an overall yield of 8%. Although ultimately successful, this initial route carried an associated shortcoming in terms of the early stage introduction of the phenyl ring *via* the aldehyde in the Pictet-Spengler step. In the event that future work required variation of this aryl substituent it was felt that such a sequence would not prove optimal.

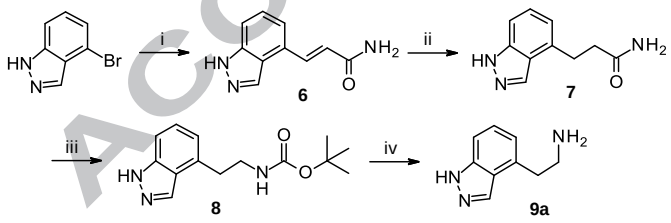
In order to address this issue, we focused on the design of an alternative approach which utilized a suitable, commercially available indazole as a starting point. Ideally the intermediate in question would be elaborated into the corresponding ethanamine, thus potentially allowing formation of the targets *via* a late stage Pictet-Spengler or Bischler-Napieralski cyclisation. Similar reactions have been carried out on a range of predominantly electron rich aryl and heteroaryl ethanamine analogues.[6] Although unable to find precedent for such chemistry on an indazole core, we were hopeful that this heterocycle would also fit into the scope of the two cyclisation methods.

To achieve our objective, a diverse set of synthetic strategies were employed to make the appropriate 'indazole-substituted ethanamine' precursors **9a-c** for use in these two approaches. The methods of ring closure were then compared to determine the most suitable route for preparing the target structures **1a-c**.

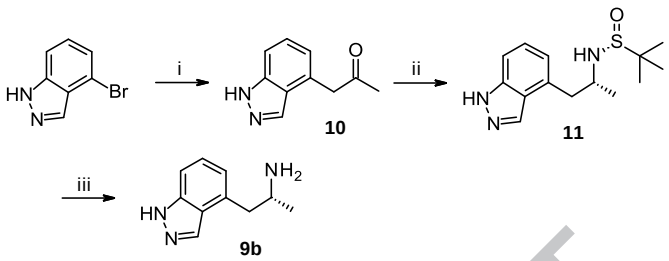
Commercially available 4-bromoindazole was identified as an appropriate starting point for synthesizing the three intermediate ethanamines **9a-c** which differed only in the nature of substitution on the carbon adjacent to the amino group.

In the route to the unsubstituted methylene analogue **9a** (Scheme 2) 4-bromoindazole was first reacted under Heck conditions with acrylamide to yield intermediate **6**. Although the yield for this step was moderate (52%), no 1,4 addition product was observed and protection of the indazole nitrogen was found to be unnecessary for this particular transformation.

Catalytic hydrogenation gave the saturated amide **7** which was then converted to the corresponding Boc protected ethanamine analogue **8** *via* a Hoffman rearrangement using lead tetraacetate in *tert*-butanol.[7] Attempts to replace lead tetraacetate with alternative reagents for this transformation, such as bis(trifluoroacetoxy)iodobenzene proved unsuccessful. Deprotection of **8** under acidic conditions then yielded 2-(1*H*-indazol-4-yl)ethanamine **9a**.



Scheme 2. Reagents and conditions: (i) acrylamide, $Pd(dtbpf)Cl_2$, TBACl, *N*-cyclohexyl-*N*-methylcyclohexanamine, MeCN, 130 °C, MW, 52%; (ii) H_2, Pd/C, EtOH, rt, 95%; (iii) $Pb(OAc)_4$, *t*-BuOH, 80 °C, 56%; (iv) TFA/CH_2Cl_2, rt, 100%.

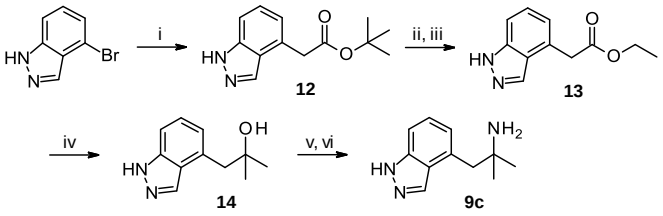


Scheme 3. Reagents and conditions: (i) $Pd(OAc)_2$, isopropenyl acetate, tributyltin methoxide, tri(*o*-tolyl)phosphine, toluene, 100 °C, 59% (ii) $Ti(i\text{-}PrO)_4$, (*R*)-*tert*-butanesulfinamide, THF, 65 °C then $NaBH_4$, -48 °C, 51% (iii) HCl, MeOH/dioxane, rt, 100%.

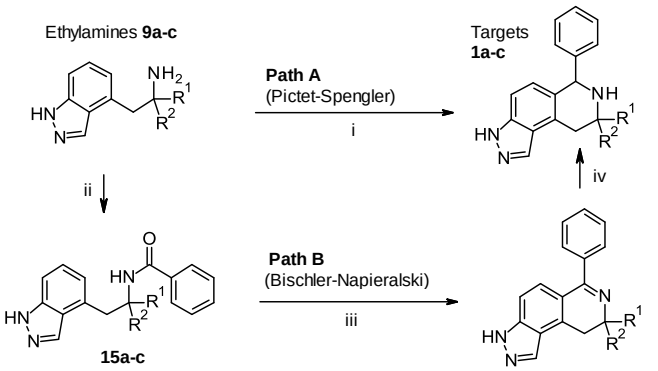
Our route to the chiral α-methyl substituted analogue **9b** (Scheme 3) commenced using 4-bromoindazole in a Stille type coupling with tributyltin methoxide and isopropenyl acetate to yield ketone **10**.[8] In order to form the desired (*R*)-1-(1*H*-indazol-4-yl)propan-2-amine **9b**, this ketone was first condensed with (*R*)-*tert*-butanesulfinamide to give the imine intermediate. *In situ* reduction of the imine with sodium borohydride then gave a 51% yield of the desired diastereoisomer **11**, following HPLC purification to remove 4% of the unwanted isomer (procedure according to Ellman and co-workers, stereochemistry assignment was based on the results therein for benzylmethyl ketone).[9] The synthesis was completed by acidic cleavage of the sulfinamide to yield analogue **9b.**

For introduction of the dimethyl substitution in target **9c** (Scheme 4) 4-bromoindazole was initially reacted under Negishi conditions with 2-*tert*-butoxy-2-oxoethylzinc chloride to form *tert*-butyl ester **12**. This intermediate was converted to the corresponding ethyl ester **13** *via* cleavage with TFA and then heating the resultant acid (not isolated) in ethanol in the presence of catalytic sulfuric acid. Formation of the tertiary alcohol **14** was achieved by treating the ethyl ester with methylmagnesium bromide.

We chose to employ a modified Ritter procedure with chloroacetonitrile[10] to access the desired 1-(1*H*-indazol-4-yl)-2-methylpropan-2-amine from alcohol **14**, the initially formed chloroamide (not isolated) being easily converted to **9c** using thiourea.



Scheme 4. Reagents and conditions: (i) 2-*tert*-butoxy-2-oxoethylzinc chloride, DavePhos, $Pd(dba)_2$, THF/toluene reflux, 49%; (ii) TFA, rt; (iii) EtOH, cat H_2SO_4, reflux, 83% (2 steps); (iv) NaH, 0 °C, THF, then MeMgBr -78 °C, 64%; (v) 2-chloroacetonitrile, AcOH, H_2SO_4, rt, 100%; (vi) thiourea, EtOH/AcOH, reflux, 56%.



Scheme 5. Reagents and conditions: (i) benzaldehyde, TFA, 130 °C, MW; (ii) benzoyl chloride, DIPEA, CH_2Cl_2/THF, rt; (iii) $POCl_3$, P_2O_5, reflux; (iv) $NaBH_4$, MeOH/THF, rt.

Table 1
Yields for Path A and Path B cyclisation routes

R^1, R^2	Path A (%)	Path B (%)
H, H (**1a**)	61	66
Me, H (**1b**)	59	44
Me, Me (**1c**)	91	-

The three 'indazole-substituted ethanamine' analogues **9a-c** prepared as described above were then assessed in the two cyclisation pathways shown in Scheme 5. Results for the Pictet-Spengler reaction (Path A) and the three step Bischler-Napieralski 'sequence' (Path B) are reported (Table 1). It should be noted that the yields quoted in Table 1 for Path B are overall yields, over the three steps (ii, iii and iv) shown in Scheme 5.

Initial efforts to react **9a** with benzaldehyde in a Pictet-Spengler cyclisation (Path A) focused on the use of mild conditions, such as stirring in dichloromethane with TFA at room temperature. Although these reagents have proved successful for converting analogous indole analogues[11] they yielded only recovered starting materials when applied to **9a**. More forcing conditions, microwave heating at 130 °C in TFA were identified as a suitable method for this step, giving **1a** in a yield of 61%.

Alternatively, using Path B, starting material **9a** could first be converted to the amide **15a** using benzoyl chloride (91%) and then cyclized using Bischler-Napieralski methodology. For the cyclisation step we resorted to heating in $POCl_3$ in the presence of P_2O_5. This resulted in an effective transformation to the intermediate dihydroisoquinoline (not isolated). A 73% yield of target **1a** from amide **15a** was obtained following reduction of the dihydroisoquinoline with sodium borohydride, giving an overall yield of 66% for these three steps from **9a** (Table 1).

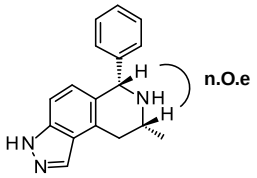
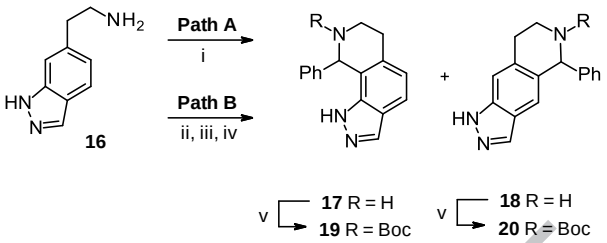


Figure 2. *Cis* stereochemistry of **1b**



Scheme 6. Reagents and conditions: (i) benzaldehyde, TFA, 130 °C, MW, 32% (**17** and **18**, mixed isomers); (ii) benzoyl chloride, DIPEA, CH_2Cl_2/THF, rt; (iii) $POCl_3$, P_2O_5, reflux; (iv) $NaBH_4$, MeOH/THF, 3 steps, 87% (**17** and **18**, mixed isomers); (v) Boc_2O, MeOH, rt, (**19**, 47% and **20**, 29%).

For substrate **9a** there was little difference between the two methods; the Bischler-Napieralski sequence gave the slightly higher overall yield (66%), whereas the shorter Pictet-Spengler step (61%) required long microwave reaction times (30 h) at elevated temperature (130 °C).

Formation of α-methyl analogue **1b** from **9b** under Pictet-Spengler conditions in TFA was also found to require a long microwave reaction time at high temperature and resulted in a similar yield of the cyclized material (59%). For this example, however, the Bischler-Napieralski sequence (Path B) gave a lower overall recovery of 44% from ethanamine **9b**, mostly due to a low conversion (49%) of amide **15b** to target **1b**. It should also be noted that for both methods the stereochemistry of the major product **1b** was confirmed by nOe experiments and shown to exhibit '*cis*' arrangement of the phenyl and methyl substituents (Fig. 2). The analogous *trans* compound (not isolated) was only observed in trace amounts in the crude reaction mixtures.

For the dimethyl substituted precursor **9c**, cyclisation *via* Path A using the same Pictet-Spengler conditions (microwave heating at 130 °C in TFA) enabled us to isolate target **1c** in 91% yield.[12] However, on this occasion we were unable to form **1c** using the Bischler-Napieralski (Path B) 'sequence'. Heating under the $POCl_3/P_2O_5$ conditions resulted in loss of nitrogen from the tertiary centre of amide **15c**, leading to decomposition of the starting material.

Having focused our initial investigations on the derivatives of 2-(1*H*-indazol-4-yl)ethanamine **9a-c** as a starting point for the Pictet-Spengler and Bischler-Napieralski cyclisations, we then attempted the same chemistry on the isomeric 2-(1*H*-indazol-6-yl)ethanamine **16** (prepared using a similar synthetic route to **9a**, see ESI), as shown in Scheme 6. On this occasion both the 'Path A' and 'Path B' cyclisation protocols resulted in a mixture of the 2 possible regioisomers (**17** and **18**) accessible from starting material **16** (Scheme 6). The Bischler-Napieralski sequence gave the better overall yield of 87 % as a 5:3 ratio of **17** to **18**, whereas from the Pictet-Spengler step we isolated 32% of a 3:1 ratio in favour of the same isomer.

The mixture of isomers obtained from the Bischler-Napieralski path was converted to the corresponding Boc protected compounds, allowing facile separation of **19** and **20** using silica gel chromatography. The structures of these two regioisomers were assigned using ^{1}H NMR (based on the observed ortho coupling for the indazole 'aryl' protons in isomer **19**).

In summary, we have reported the synthesis of a small set of 8-substituted-6-phenyl-,7,8,9-tetrahydro-3*H*-pyrazolo[4,3-*f*]isoquinolines. The strategy of constructing this scaffold *via* either Pictet-Spengler or Bischler-Napieralski cyclisation methodology proved successful and to the best of our knowledge represents the first reported examples of these traditional reactions on an indazole core. For the ethanamine analogue lacking substitution on the carbon adjacent to the amino group (**9a**) there was little to choose between the two routes under

consideration. For mono (**9b**) or dimethyl (**9c**) substituted structures, our preferred cyclisation conditions favoured formation of the targets *via* the Pictet-Spengler reaction.

Acknowledgments

We would like to thank Howard Beeley, Paul Davey, Scott Boyd, David Whittaker and Peter Barton for analytical support.

Supplementary Data

Supplementary material (experimental procedures and characterization data including ^{1}H NMR, ^{13}C NMR spectra for all isolated compounds) associated with this article can be found in the online version.

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12. This Pictet-Spengler approach was used to react **9c** with 4-bromo-2-fluoro-6-methoxybenzaldehde to give the corresponding tricyclic indazole in 88% yield. For details see PCT Int. Appl. (2017), WO2017182495, 166 pp.

Graphical Abstract

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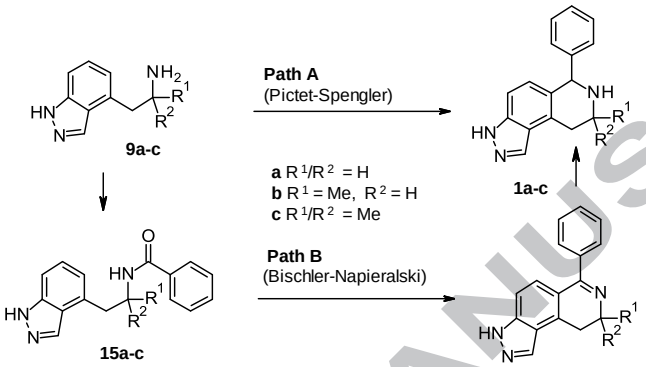

HIGHLIGHTS

Pictet-Spengler or Bischler-Napieralski used to construct a tricyclic indazole core
Conditions develop to allow indazoles to undergo these cyclisations
Cis stereochemistry prefered in the case of α-methyl indazole ethanamines