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Radical cyclisation onto pyrazoles: synthesis of withasomnine

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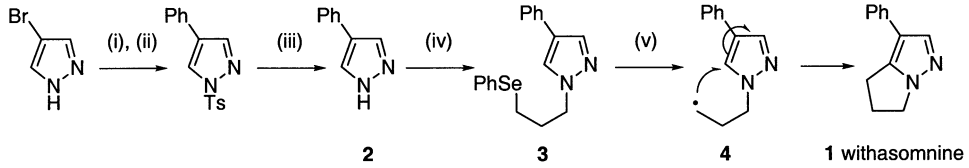
Abstract—A novel synthetic protocol for the synthesis of [1,2-*b*]-fused bicyclic pyrazoles has been developed using radical cyclisation. The protocol uses cyclisation of pyrazole-1-(ω-alkyl) radicals generated from 1-[ω-(phenylselenyl)alkyl]-pyrazole precursors. The pyrazole natural product, withasomnine (3-phenyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole), and larger ring analogues have been synthesised in good yield using the protocol. A Bu_3SnH-mediated oxidative cyclisation mechanism is facilitated by azo or Et_3B radical initiators acting as oxidants of the intermediate π-radicals.

The synthesis of nitrogen heterocycles using radical intermediates has become a common protocol in modern organic chemistry.[1] Radical cyclisation using tributyltin hydride (Bu_3SnH) as the radical generating agent with a radical initiator has been commonly used. In these reactions a cyclised reduced product is produced by the standard radical chain mechanism wherein Bu_3SnH acts as a radical generator of the initial radical prior to cyclisation and reductant of the cyclised radical. However, cyclisations onto aromatic rings yield relatively stable π-radicals which are not reduced by Bu_3SnH and are oxidised by loss of hydrogen ($H^{\bullet}$) in a rearomatisation process. Many of these reactions can be considered to be the *umpolung* of Friedel–Crafts alkylation, i.e. alkylation of electron-deficient heteroarenes using nucleophilic radicals as opposed to Friedel–Crafts alkylation of electron rich heteroarenes using cationic electrophiles. These cyclisations are regioselective and hence allow rational synthetic planning of target molecules. In synthetic considerations the overall protocol can be considered to be a homolytic aromatic substitution.[2]

In our earlier studies we have reported the Bu_3SnH-mediated 'oxidative' cyclisation of *N*-(ω-alkyl)-radicals onto pyrroles and imidazoles with electron withdrawing groups.[3] More recently, we have shown that acyl radicals undergo cyclisation onto electron deficient pyrroles with 2- and 3-substituted electron withdrawing groups.[4] Recent references for this protocol also include oxidative cyclisation onto indoles,[5] pyridines,[6] 1,2,3-triazoles[7] and pyridones.[8] Heterocycles have also been synthesised using this radical protocol wherein the heteroatom is in the cyclising chain with cyclisation onto arenes rather than heteroarenes, e.g. 6*H*-benzo[*c*]chromenes,[9] oxindoles[10] and acridines.[11]

No radical cyclisation studies involving pyrazoles have been reported which is surprising because of the considerable interest of pyrazoles to the pharmaceutical indus-



Scheme 1. Synthesis of withasomnine. *Reagents and conditions*: (i) NaOH, TsCl, DCM, 24 h, rt (98%); (ii) $PhB(OH)_2$ (1.1 equiv.), aq. K_2CO_3, DME, $Pd(PPh_3)_4$ (0.1 equiv.), reflux, 24 h (77%); (iii) NaOH (5 M), H_2O, MeOH (98%); (iv) $PhSe(CH_2)_3I$ (1.2 equiv.), KOH (3 equiv.), DMF (100%); (v) Bu_3SnH (1.3 equiv.), ACCN (2 equiv.), toluene, reflux, 4 h (38%).

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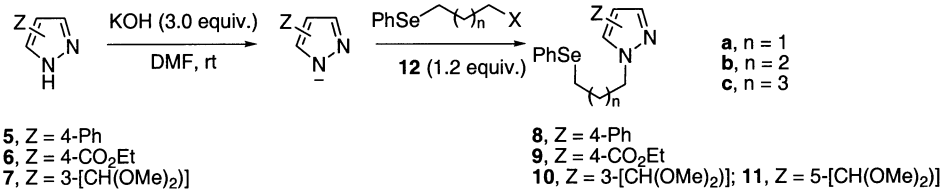
try because of their biological activity. There is also no general method for the synthesis of bicyclic pyrazoles. In this communication we report a novel protocol for the synthesis of [1,2-*b*]-fused bicyclic pyrazoles. These studies are the first radical cyclisations onto pyrazole rings. The application of these synthetic studies to the synthesis of withasomnine (3-phenyl-5,6-dihydro-4*H*-pyrrolo-[1,2-*b*]pyrazole) **1**, one of a very small number of pyrazole natural products, is shown in Scheme 1. Withasomnine **1** was first isolated from *Withania somnifera* (*Solanaceae*) 26 years ago[12] and has been synthesised by various routes[13] but none have involved radical chemistry. Withasomnine and analogues continue to be isolated from natural sources[14] and plant extracts which contain withasomnine are used in Ayervudic alternative medicine and are claimed to cure a large range of ailments.

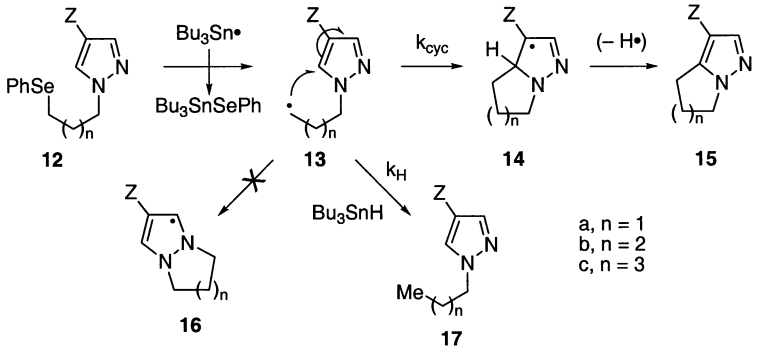
Scheme 1 illustrates the protocol for the radical cyclisation onto pyrazoles. In this synthesis of withasomnine **1**, 4-phenylpyrazole **2** was alkylated to yield the radical precursor **3** which undergoes oxidative cyclisation via the intermediate radical **4**. 4-Phenylpyrazole was synthesised in high yield by a Suzuki coupling from the tosyl-protected 4-bromopyrazole. The only low yielding step (38%) is the radical cyclisation. 5-*exo* Radical cyclisations onto 5-membered ring heteroarenes have severely strained transition states and previous studies have also illustrated this problem.[3,4,15] The structure of withasomnine **1** was confirmed by X-ray crystallography which also showed the alicyclic ring to be very strained and completely planar.

The radical protocol with pyrazoles was further studied with several ring-substituents [Ph, CO_2Et and $CH(OMe)_2$] and 5-, 6- and 7-*exo* cyclisations. The required radical precursors were prepared by alkylation of the *NH*-pyrazoles in high yields except for 1*H*-pyrazole-4-carboxylic acid ethyl ester **6** which gave some ester hydrolysis (Scheme 2). Alternative protocols to avoid the hydrolysis were not studied. Phenylselenyl precursors[3] were used in order to avoid problems of intramolecular alkylation on side chain ω-halides by the basic 'pyridine' nitrogen of pyrazole. Phenylselenide ($PhSe^-$) is a poor leaving group and precludes this problem. As expected, alkylation of 3-dimethoxymethyl-1*H*-pyrazole **7** gave mixtures of 3- and 5-dimethoxymethyl-pyrazoles due to the ambident nature of the pyrazole anion with predominant regioselectivity towards the 3-isomer.

For both pyrazoles (Z = Ph and CO_2Et) the six-membered ring cyclisation is most favourable because of less strain than the 5-membered ring cyclisation and less entropy problems than the 7-membered ring cyclisation, as has been observed for other cyclisations onto heteroarenes.[3,4] For $Z = CO_2Et$, the 5- and 7-membered ring cyclisations were unfavourable and only reduced products **17** ($Z = CO_2Et$) were obtained which indicates that stabilisation by the intermediate π-radical **14** by phenyl is more effective than CO_2Et. For $Z = CO_2Et$, the cyclisations carried out with Bu_3SnH were less favourable due to faster H-abstraction of hydrogen by intermediate radicals. The intermediate radicals **13** (Z = Ph and CO_2Et) showed complete regioselectivity of cyclisation onto the 5-C on the pyrazole ring and no products resulting from cyclisation onto the 2-N (via **16**) were observed (Scheme 3).



Scheme 2. Alkylation of substituted pyrazoles. **5**: **12a** (X = I), 24 h, **8a** (100%); **12c** (X = I), 24 h, **8c** (98%). **6**: **12a** (X = I), 40 h, **9a** (24%); **12b** (X = I), 28 h, **9b** (55%); **12c** (X = Cl), 28 h, **9c** (35%). **7**: **12a** (X = I), 36 h, **10a** (31%), **11a** (52%); **12b** (X = Cl), 28 h, **10b** (50%), **11b** (34%); **12c** (X = Cl), NaI (0.2 equiv.), 36 h, **10c** (60%), **11c** (29%).



Scheme 3. Cyclisation of 4-phenylpyrazoles and ethyl pyrrole-4-carboxylates. **12**, Z = Ph, Bu_3SnH (1.3 equiv., added by syringe pump), ACCN (1.5 equiv.), toluene, reflux, 4 h: $n = 1$, **15a** (38%), **17a** (17%); $n = 2$, **15b** (63%), **17b** (0%); $n = 3$, **15c** (37%), **17c** (48%). **12**, $Z = CO_2Et$, $(TMS)_3SiH$ (1.3 equiv.), Et_3B (1.5 equiv.), cyclohexane, rt, air, 8 h, followed by addition of the same amount of $(TMS)_3SiH$ and Et_3B, 12 h: $n = 1$, **15a** (0%), **17a** (73%); $n = 2$, **15b** (36%), **17b** (0%); $n = 3$, **15c** (0%), **17c** (62%).

The mechanism of the oxidative step (**14** to **15**) is not clear but the stability of the stable π-radical intermediate (e.g. **14**) is crucial.[2–4,7,9] Reduction by H-abstraction from Bu_3SnH or $(TMS)_3SiH$ is unfavourable which allows time for interception by the radical initiator ACCN (in Bu_3SnH reactions) or a radical breakdown product from ACCN or Et_3B in respective reactions. Evidence indicates H-abstraction from the π-radical intermediates.[4,9] For the Et_3B reactions the abstracting radical is probably ethyl radical generated in the oxygen-induced breakdown of Et_3B. The reactions using ACCN needed greater than one equivalent of the radical initiator indicating involvement of ACCN or breakdown products (e.g. 1-cyanocyclohex-1-yl radicals) as has been observed in most of these Bu_3SnH-mediated 'oxidative' cyclisations.[2–11] An alternative mechanism involving addition of 2-cyanoprop-2-yl radicals (resulting from AIBN) to the π-radical followed by non radical elimination has also been proposed.[5]

In contrast, the attempted cyclisation reactions with radical precursors **10a**–**c** which have a 3-dimethoxymethyl substituent, only yielded reduced uncyclised products. Even the most favoured six-membered ring cyclisation from precursor **10b** failed. This cyclisation was attempted with both Bu_3SnH and the slower $(TMS)_3SiH/Et_3B$ protocol at room temperature. We suggest that unlike the 4-Ph and 4-CO_2Et substituents, the 3-dimethoxymethyl substituent does not stabilise the potential cyclised radical and hence cyclisation is unfavourable.

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