Pergamon

Tetrahedron Letters 41 (2000) 8173–8176

TETRAHEDRON LETTERS

A novel synthesis of spirocyclic pyrrolidin-2-ones

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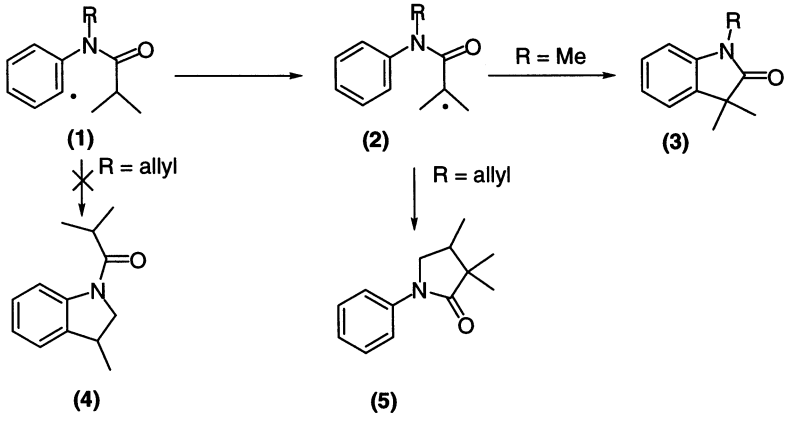
Received 31 July 2000; revised 18 August 2000; accepted 23 August 2000

Abstract

A short synthesis of a series of spirocyclic pyrrolidin-2-ones is presented which proceeds via initial [1,5]-radical translocation followed by cyclisation.

Keywords: cyclisation; radical translocation; nitrogen heterocycles; spirocycles.

It is well known that radicals will readily take part in intramolecular hydrogen atom transfer reactions, with examples of [1,4]-,[1] [1,5]-,[2] [1,6]-,[3] and [1,7]-[3b,c,d,e] transfers being documented. These processes represent a convenient method to activate selectively a remote site within a molecule for a bond forming reaction to take place subsequently. Our interest in this area has centred upon the reaction of aryl radicals **1** (Scheme 1) generated from suitable halo anilides. In



Scheme 1.

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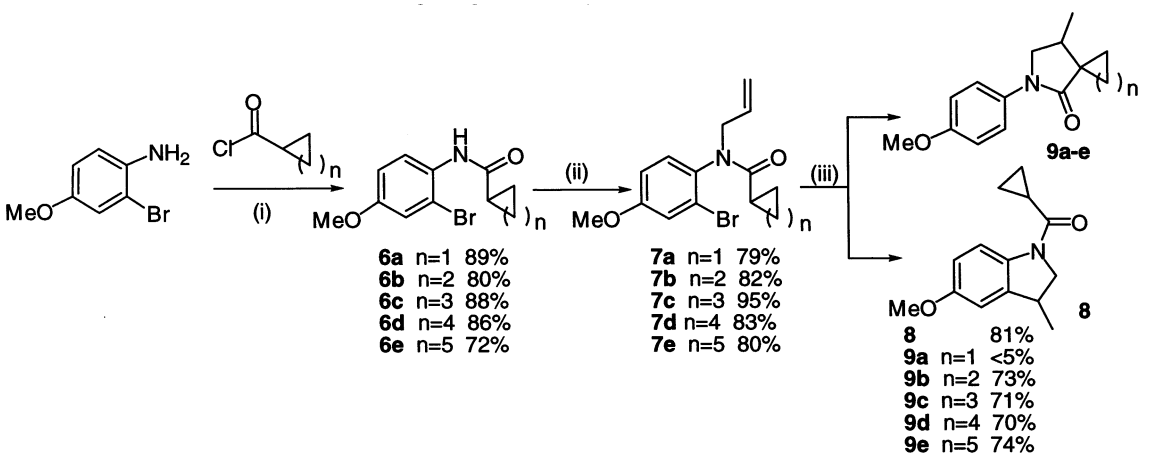
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01426-X

cases where R = CH_3, these highly reactive aryl radicals underwent 1,5-hydrogen atom transfer to give a new, stabilised, tertiary radical **2**. This radical then took part in a homolytic aromatic substitution to give predominantly oxindole **3**.[4] In cases where R = allyl, once again [1,5]-hydrogen atom abstraction occurred to give radical **2** (in preference to direct cyclisation to give dihydroindole **4**) and this was followed by 5-*exo trig* cyclisation onto the allyl double bond giving pyrrolidinone **5**.[5]

It was of interest to explore further this tandem hydrogen atom abstraction/cyclisation process for the synthesis of spirocyclic pyrrolidin-2-ones. These compounds have been shown to exhibit some interesting biological properties,[6] as well as being part of the core ring system found in a number of interesting natural products such as polyzonimine[7a] and the kopsia alkaloids.[7b]

In order to develop the synthetic potential of the tandem process outlined in Scheme 1, removal of the aryl group after cyclisation is a primary requirement. In doing this the aryl group will be acting as a protecting/radical translocating group, a protocol that has been used to good effect in a number of previous applications involving the *o*-bromo-*p*-methoxyphenol group.[2d]

The synthesis of the required cyclisation precursors was straightforward and was achieved by reacting the appropriate acid chloride with 2-bromo-4-methoxyaniline followed by *N*-allylation using sodium hydride and allyl bromide (Scheme 2), giving **7a–e** in good yield.

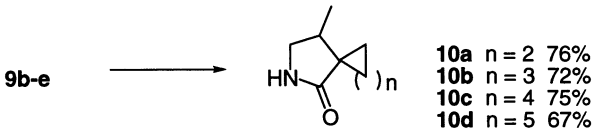


Scheme 2. **Reagents and conditions**: (i) *N*,*N*-diisopropylethylamine (1.05 equiv.), diethyl ether, 20°C, 6 h; (ii) NaH (1.05 equiv.), allyl bromide (1.1 equiv.), THF, 8 h; (iii) Bu_3SnH (1.1 equiv.), AIBN (0.2 equiv.), toluene, 110°C, 2 h

Treatment of **7a–e** with tributyltin hydride (TBTH) (0.04 M) under standard radical conditions (syringe pump addition of the TBTH was unnecessary) gave good to excellent yields of the spirocyclic pyrrolidin-2-ones **9b–e**.[8] Careful examination of the crude NMR spectra of the cyclisation products **9b–e** showed small amounts of product arising from direct cyclisation of the aryl radical onto the allyl double bond.[9] The main product however resulted from [1,5]-hydrogen atom transfer followed by 5-*exo trig* cyclisation. A small amount of 6-*endo trig* cyclisation (<5%) was also observed. To explore the possibility of any competing [1,6]- or [1,7]-hydrogen abstraction occurring, tributyltin deuteride was used for the reaction of substrate **7c**. The ^2H NMR spectra showed no indication of either Ar–D (due to direct reduction of the aryl radical) or deuterium incorporation in the cyclopentyl ring. The only deuterated product that was detected arose from quenching of the methyl radical after cyclisation. Interestingly, the reaction

of the cyclopropyl precursor **7a** gave <5% of the desired spirocyclic product **9a**, and gave almost exclusively the dihydroindole **8** arising from direct cyclisation of the aryl radical onto the allyl bond. Presumably, this outcome is the result of the greater bond strength of a cyclopropyl carbon–hydrogen bond compared with the carbon–hydrogen bond strengths in the other substrates, which makes [1,5]-hydrogen atom abstraction less efficient.

In order to complete the synthesis of the spirocyclic pyrrolidin-2-one systems, oxidative removal of the *p*-methoxyphenyl protecting group was investigated. This proved straightforward and was achieved by treatment of a solution of the spirocyclic pyrrolidin-2-one in acetonitrile with an aqueous solution of ceric ammonium nitrate[10] to give the spirocyclic lactams **10a–d** in good yield (Scheme 3).



Scheme 3.

In summary, an aryl radical has been used to generate an alkyl radical at an unfunctionalised site. The cyclisation of this alkyl radical onto an appropriately situated carbon–carbon double bond gives spirocyclic pyrrolidin-2-ones from which the *N*-aryl group can be removed. This tandem [1,5]-hydrogen atom abstraction/cyclisation protocol is both short and high yielding.

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8. Typical experimental procedure: tributyltin hydride (379 mg, 1.30 mmol) and azoisobutyronitrile (10 mg) were added to a solution of **7c** (400 mg, 1.18 mmol) in toluene (50 ml). The reaction mixture was heated at 110°C for two hours, cooled, poured into ether, and washed with ammonia solution (10%). The ether solution was dried

with magnesium sulfate, concentrated, and the crude product purified by column chromatography on silica (ethyl acetate/hexane, 3:1) to give **9b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, d, *J* 6.9, *Me*), 1.60 (7H, m, cyclopentyl-H), 1.99 (1H, m, cyclopentyl-H), 2.16 (1H, m, H-4), 3.23 (1H, dd, *J* 7.1, 9.4, H-5), 3.68 (1H, dd, *J* 7.1, 9.4, H-5), 3.71 (3H, s, O*Me*), 6.82 (2H, d, *J* 9.1, Ar*H*), 7.49 (2H, d, *J* 9.1, Ar*H*); ^{13}C NMR (75 MHz) δ 14.1 (CH_3), 26.14 (cyclopentyl CH_2), 26.42 (cyclopentyl CH_2), 30.33 (C-4), 36.06 (cyclopentyl CH_2), 37.48 (cyclopentyl CH_2), 53.81 (C-5), 55.88 (O*C*H_3), 56.67 (C-3), 114.27 (Ar–CH), 121.42 (Ar–CH), 133.68 (Ar–C), 156.45 (Ar–C), 179.47 (C=O). *m*/*z* (EI) found 259.1574, $C_{16}H_{21}NO_2$ requires 259.1572.

9. Ongoing investigations have shown that in similar systems when the newly formed radical is 2° a higher proportion of direct cyclisation results, indicating a less efficient [1,5]-radical translocation reaction.
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