Trifluoroacetic Acid-Promoted Synthesis of 3-Hydroxy, 3-Amino and Spirooxindoles from α -Keto-*N*-Anilides

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Ketoanilides containing alkyl side chains were readily cyclized to 3-hydroxy-2-oxindoles or spirooxindoles by a single or double intramolecular Friedel—Crafts reaction in the presence of trifluoroacetic acid (TFA) at room temperature or at 45 °C. α-Iminocarboxamides, generated in situ from ketoamides, cyclized similarly to 3-aminooxindoles under identical conditions.

3,3-Disubstituted oxindoles are structural subunits found in a wide range of natural and synthetic compounds that display interesting biological and pharmacological properties.¹ Consequently, a number of elegant synthetic strategies have been developed for the synthesis of this class of heterocyle.² Recently, diversely *ortho*-prefunctionalized α -ketoanilides (boronate,³ halide⁴) have been converted to 3-hydroxyoxindoles through metal-catalyzed cyclization processes.

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Cyclization of α -ketoamides by way of an intramolecular Friedel–Crafts reaction is an attractive way for the synthesis of 3-hydroxyoxindoles.⁵ However, this approach was limited essentially to the synthesis of 3-aryl containing oxindoles. Indeed, competing enolization and/or

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⁽⁶⁾ Under super acid reaction conditions, alkyl-substituted α -ketoamides produced α , β -unsaturated amides; see ref 5b.

⁽⁷⁾ Formation of 3-methylene oxindoles from 3-hydroxy oxindoles is well precedented, see for example: Munusamy, R.; Dhathathreyan, K.; Balsubramanian, K. K.; Vankatachalan, C. S. J. Chem. Soc., Perkin Trans. 2 2001, 1154–1166.

dehydration of the resulting tertiary alcohol can completely suppress the formation of 3-alkyl containing oxindoles⁶ or prevent the isolation of 3-hydroxy oxindoles⁷ when using β -alkylated ketoamides.⁸

In connection with our general interest in oxindole synthesis⁹ and the development of strategies starting from unfunctionalized anilides,¹⁰ we decided to evaluate the possibility of building spirooxindoles **1** in a tandem fashion¹¹ by performing a double cyclization of α -ketoa-nilides with concurrent generation of all-carbon quaternary center (Nu = π -nucleophile) as depicted in Scheme 1.¹² We report herein that, under acidic conditions, intramole-cular Friedel–Crafts reaction of **3** takes place readily to afford 3-alkyl(aryl)-3-hydroxy-2-oxindoles **2**. With an appropriately tethered nucleophile, a second cyclization occurred to directly provide the spirooxindoles **1**. In addition, we document that 3-amino-oxindoles can be prepared from the corresponding α -ketoamides under identical conditions.

Scheme 1. Double Cyclization Sequence for the Synthesis of Spiro-2-oxindole



We selected *N*-methyl-2-oxo-*N*-phenylbutanamide (4a) as a model substrate for the survey of reaction conditions (Scheme 2). While AcOH was inefficient for promoting the cyclization even at 45 $^{\circ}$ C, we found that the desired cyclization proceeded readily at room temperature in the presence of trifluoroacetic acid (TFA). In pure TFA, the reaction was complete within 6 h, whereas in a mixture of

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(10) (a) Wei, H.-L.; Piou, T.; Dufour, J.; Neuville, L.; Zhu, J. Org. Lett. **2011**, 13, 2244–2247. (b) Jaegli, S.; Dufour, J.; Wei, H.-L.; Piou, T.; Duan, X.-H.; Vors, J.-P.; Neuville, L.; Zhu, J. Org. Lett. **2010**, 12, 4498– 4501. solvents (DCM/TFA or tol/TFA, v/v = 1/1), a longer reaction time (24 h) was needed to reach completion.¹³ At higher concentration (c 0.9 M), a dimerization product **6a** was produced together with **5a**. However, the dimer was formed only in a trace amount at c = 0.4 M and was not detected at c = 0.09 M. We also noticed the formation of a variable amount of trifluoroacetate **5b** (R = CF₃CO, 5-10% and up to 40% yield for some other substrates). This product is readily hydrolyzed to **5a** (R = H) upon workup with aqueous NaOH solution before extraction. Overall, under our optimized conditions [TFA, c 0.09M, rt, 6 h, then aqueous NaOH (3N) at rt for 1 h], cyclization of **4a** afforded **5a** in 94% yield.



The scope of this process was next examined (Table 1). The reaction was found to be general leading to the expected 3-hydroxy-2-oxindoles in yields ranging from 50 to 94%. Notably and in sharp contrast to other related literature work, diverse alkyl side-chains, such as methyl, ethyl, isobutyl, and phenethyl, were tolerated. As expected, aryl-substituted α -ketoamide 4h was an excellent substrate, furnishing the corresponding 3-phenyl-3-hydroxy-2-oxindole (5h) in 83% yield. A tertiary amide was mandatory for the cyclization, as no oxindole was formed in the case of 2-oxo-N-phenylbutanamide (not shown). N-Benzyl derivative 4i afforded oxindole 5i in 58% yield, indicating that the benzyl residue did not participate in the cyclization reaction. Cyclization of a tetrahydroquinoline derivative 4j furnished tricyclic oxindole 5j in 85% yield (entry 9). Substituted anilides bearing electron-donating groups at the para-position (OMe, Me) cyclized smoothly to generate the expected oxindoles 5d, 5g and 5h (entries 3, 6 and 7). The presence of a weak electron-withdrawing group (chlorine) at the para-position of anilide was also tolerated furnishing compound 5e in an excellent 89% yield. Gentle heating (45 °C) and longer reaction time were however required in this case in order to drive the reaction to completion.

Anilides containing a functionalized alkyl side chain such as a bromoalkyl or a secondary hydroxyl group were compatible with the reaction conditions (Scheme 3). Treatment of 3-bromo-*N*-methyl-2-oxo-*N*-phenylpropanamide

 ⁽⁸⁾ For a recent enantioselective synthesis of 3-alkyl-3-hydroxy-2-oxindole from *ortho* functionalized α-ketoanilides, see: Yin, L.; Kanai, M.; Shibasaki, M. Angew. Chem., Int. Ed. 2011, 50, 7620–7623.

⁽¹¹⁾ For general reviews on the domino process, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. For a monograph, see: (b) *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K., Eds.; Wiley-VCH: Weinheim, 2006.

⁽¹²⁾ For a recent review on Friedel–Crafts reaction, see: Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527–3544.

⁽¹³⁾ For the benficial effect of performing Friedel–Crafts processes in concentrated or pure TFA, see: (a) Youn, S. W.; Bihn, J. H. *Tetrahedron Lett.* **2009**, *50*, 4598–4601. (b) Wu, Y.-C.; Liu, L.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. J. Org. Chem. **2007**, *72*, 9383–9386. (c) Ma, S.; Zhang, J. *Tetrahedron* **2003**, *59*, 6273–6283.

4k under standard conditions, without basic aqueous workup, afforded 3-(bromomethyl)-3-hydroxy-2-oxindole 5k in 76% yield. On the other hand, upon basic aqueous workup, a second cyclization took place leading to spiroepoxyoxindole 7 in 67% yield.¹⁴ Therefore, by simply modifying the workup procedure, we were able to obtain two sets of heterocycles that can in principle be further functionalized in different ways.¹⁵ Cyclization of TBSprotected N-methyl (S)-3-hydroxy-2-oxo-N-phenyl butanamide¹⁶ (41) occurred smoothly, furnishing the deprotected diol 51 in 80% yield. A modest but significant diastereselectivity (dr = 3.5/1) was observed. Analysis of SFC traces (IB column) of 5l and ent-5l, obtained by cyclization of (S)-4l and (R)-4l, respectively, allowed us to conclude that no epimerization occurred during the cyclization (see Supporting Information). We have also examined the role of the hydroxy protective group on the diastereoselectivity of this cyclization. When (R)-4m (R =TBDPS) was submitted to the cyclization, the deprotected diol ent-51 was again obtained but with increased diastereoselectivity (dr = 4.5/1). On the other hand, cyclization of unprotected alcohol (R)-40 afforded ent-51 as a 2/1 mixture of diasteromers. These results indicated that when (R)-41 (R = TBDMS) and (R)-4m (R = TBDPS) were submitted to our cyclization conditions, partial O-deprotection occurred before cyclization and that much better diastereoselectivity could be expected if a bulky but acid-stable *O*-protective group was installed in **40**.¹



We next turned our attention to the synthesis of spirooxindoles through a double intramolecular

(17) We thank reviewers for suggesting these control experiments.

Table 1. Synthesis of 3-hydroxy-2-oxindoles: substrate scope





^{*a*} General conditions: **4** in TFA (C = 0.09 M), rt then NaOH (3.0 M) up to pH = 13. ^{*b*} Isolated yield. ^{*c*} At 45 °C. ^{*d*} Basic workup with 3.0 N NaOH was not required.

Friedel–Crafts reaction of α -ketoamides bearing a tethered arene.¹⁸ The reactivity of compound **8a** (R = H, n =

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⁽¹⁵⁾ Structural diversity derived from work-up procedure, see: Gámez-Montaño, R.; González-Zamora, E.; Potier, P.; Zhu, J. *Tetrahedron* **2002**, *58*, 6351–6358.

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⁽¹⁸⁾ Two-step synthesis of 3,3'-alkyl-aryl oxindoles has been documented, see: England, D. B.; Merey, G.; Padwa, A. *Org. Lett.* **2007**, *9*, 3805–3807. *N*-methyl oxindoles were found to be unsuitable substrates under their conditions, see ref 23 of this work.

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Scheme 4. Synthesis of Spirooxindoles 1 by Double Intramolecular Arylation of α -Ketoanilides



2, Scheme 4) was initially evaluated and we were delighted to isolate spirooxindole 1a in 87% yield upon exposure of 8a to TFA (0.04 M, 45 °C, 24 h). The 4-methoxy and 4-chloro-substituted anilides (8b, 8c) underwent spirocyclization smoothly to afford tetracyclic compounds 1b and 1c in yields of 95 and 73%, respectively. The reaction was not limited to the formation of spiro tetrahydronaphthalenes, as 5- and 7-membered carbospirocycles 1d-1g were also formed under similar conditions. The reduced yield of spiroindene 1d can be accounted for by the competitive dimerization/polymerization of the hydroxyoxindole intermediate.¹⁹ Such a competitive pathway was markedly reduced when 4-substituted anilides were used leading to 1e in 62% yield. The yields of the seven-membered spirooxindoles 1f and 1g (64 and 69%, respectively) were quite remarkable as a related intramolecular S_EAr reaction of 3-bromoindolin-2-one produced the cyclic product in only 13% yield.²⁰

The 3-aminooxindoles have recently been proven to be of interest in medicinal chemistry.²¹ Having established conditions for the synthesis of 3-hydroxyoxindoles by the Friedel–-Crafts reaction, we reasoned that the 3-amino-2-oxindoles could be similarly synthesized from α -iminocarboxamides which could, in turn, be generated in situ from α -ketoamides.

The synthesis of compound **9a** ($R = PhCH_2CH_2$, Scheme 5) was easily achieved by heating phenethylamine with α -ketoamide **4a** in toluene at reflux for 18 h.²² A substoichiometric amount of acid (0.5 equivalent of TFA) was required to effectively promote the formation of compounds **9b** (R = Bn) and **9c** (R = Ph) from the corresponding amine. Evaporation of the volatile, followed by stirring the crude iminocarboxamides in pure TFA at 45 °C for 4 h, provided the corresponding 3-aminooxindoles **10** in yields ranging from 59 to 90%. Neither 1,2,3,4-tetrahydroisoquino-line-1-carboxamide **11a** nor isoindoline-1-carboxamide **11b** via Pictet–Spengler reaction were produced in the reaction.²³ A 5-*exo*-trig cyclization mode leading to oxindoles might be kinetically more favorable than the alternative 5-*endo*-trig or 6-*endo*-trig processes encountered in the Pictet–Spengler reaction. The aniline derived product **10c** was found to be stable, and the possible Hofmann–Martius rearrangement was not observed under our reaction conditions.²⁴

Scheme 5. Synthesis of 3-Amino-2-oxindoles



In summary, we have demonstrated the utility of the intramolecular Friedel–Crafts reaction for the synthesis of diversely functionalized 3,3'-disubstituted oxindoles and spirooxindoles from readily accessible α -keto-*N*-arylace-tamides bearing alkyl side chain residues. In TFA, α -ketoanilides **4** cyclized readily at room temperature to afford the 3-hydroxy-3-alkyl(aryl)-2-oxindoles **5**, while α -iminocarboxamides **9**, prepared in situ from α -ketoa-mides, cyclized under similar conditions to 3-amino-3-alkyl-2-oxindoles **10** in good to excellent yield. From an appropriately functionalized substrate **8**, a double cyclization took place leading to spirooxindoles **1** with the creation of an all carbon chiral quaternary center.

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Supporting Information Available. Supporting Information for this article, including experimental procedures, product characterization and copies of the ¹H and ¹³C NMR spectra of all reported oxindoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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