SYNTHESIS OF OXINDOLES BY THE NAFION-H CATALYSED DECARBOXYLATIVE CYCLIZATION OF α-CARBOMETHOXY-α-DIAZOACETANILIDES

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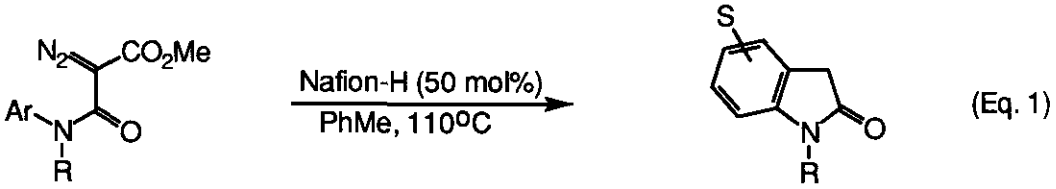
Abstract-Diazoanilides (**1**), possessing electron-donating and electron-withdrawing groups in the aromatic ring, undergo Nafion-H catalysed decarboxylative cyclization to directly give highly functionalized oxindoles in moderate yields (39–79%).

The oxindole ring system is a common structural unit found in alkaloids[1] and medicinally important compounds,[2] and its derivatives are also synthetically useful intermediates.[3a] In spite of the many documented synthetic methods for the preparation of oxindoles,[3] the Gassman protocol[4] for oxindole synthesis has found general application due to the ready availability of the starting material and mildness of the reaction conditions. However, this method required three steps which consists of the preparation of a relatively unstable amino ester, an acid-catalysed cyclization of the intermediary amino ester and Raney nickel desulfurization of the cyclized product. More direct methods for the synthesis of this important ring system would be valuable. Recently, it was reported that 3-unsubstituted oxindoles were readily prepared by the rhodium(II) acetate catalysed cyclization of α-diazoacetanilides.[5] Interestingly, the same cyclization was also catalysed by Nafion-H,[5a] which suggests that this catalyst is a suitable substitute for rhodium(II) acetate. In connection with our work on the rhodium(II) acetate catalysed reaction of α-carbomethoxy-α-diazoacetanilides,[6] we now report that the diazoanilides (**1**) undergo an unprecedented, Nafion-H decarboxylative cyclization to directly give 3-unsubstituted oxindoles.

We found that when compound (**1a**) (Eq. 1) was treated with 500 mg (50 mol%/mmol of diazoanilide) of Nafion-H in refluxing toluene for 20 h, the oxindole[7] (**2a**) was obtained in 68% yield. In the absence of Nafion-H, the reaction required a longer time (36 h) and the yield of (**2a**) was only 37%. To assess the generality of the reaction, a preliminary survey of the cyclization of a series of diazoanilides was conducted and, the results are shown in Table I.



(Eq. 1)

1 a; R= Me, Ar= 4-MeOPh **2 a**; R= Me, S= 5-MeO

As revealed in the Table, the compounds with strong electron-donating groups in the aromatic ring react efficiently to give only or predominantly[8] the oxindoles (Entries 1-4) and in moderate yields (67–79%). For the compound possessing a weak electron-donating methyl group (Entry 8), a lower yield (52%) of the oxindole was obtained. The cyclization was not impeded by the presence of an electron-withdrawing ester group in the aromatic ring (Entry 10) and there was no significant lowering of the yield of the oxindole (57%, compare Entries 8 and 10). However, it was found that the reaction required a longer reaction time (28 h) and a small amount of starting diazoanilide (6%) was recovered. Interestingly, the diazoanilides possessing a substituent ortho to the amide unit generally lead to lower yields of oxindole products (compare Entries 4/6, 5/7 and 8/9). This may be attributed to steric factors: unfavorable interaction between the N-substituent and an ortho-substituent which would destabilize the reactive conformer in the transition state that leads to oxindole formation (Entry 9). In the case of Entries 6 and 7, the additional steric hindrance present at the site of the cyclization, due to the meta-methoxy group would result in further retardation of the reaction.[9]

Table I. Nafion-H Catalysed Decarboxylative Cyclization.

	Diazoanilide (**1**)		Oxindole (**2**)	
Entry	Ar	R	S	Yield (%)[a]
1	3,4-DiMeOPh	Bu	5,6-DiMeO	79[b,c]
2	3,4-DiMeOPh	CH_2Ph	5,6-DiMeO	71[b,d]
3	4-MeOPh	Bu	5-MeO	68
4	4-MeOPh	$(CH_2)_2CO_2Me$	5-MeO	67
5	3,4-DiMeOPh	$(CH_2)_3OSiMe_2Bu^t$	5,6-DiMeO	55[b,e,f]
6	2,5-DiMeOPh	$(CH_2)_2CO_2Me$	4,7-DiMeO	31
7	2,5-DiMeOPh	$(CH_2)_3OSiMe_2Bu^t$	4,7-DiMeO	39
8	4-MePh	CH_2Ph	5-Me	52
9	2-Br-4-MePh	Et	5-Me-7-Br	36
10	4-CO_2MePh	Bu	5-CO_2Me	57

a) Yields refer to isolated yields of chromatographically pure compounds. b) Mixture of para and ortho isomers. c) para:ortho = 15:1 d) para:ortho = 5.4:1.0. e) para:ortho = 17.0:1.0. f) 9% of desilylated compound was also isolated.

The decarboxylative cyclization reaction also showed a strong preference for cyclization para to an electron-donating group in cases where ortho attack is also possible (Entries 1, 2 and 5). In addition, the reaction conditions are mild and functional groups such as an ester (Entries 4 and 10), a bromine (Entry 9) and the *t*-butyldimethylsilyl ether (Entry 5) groups are tolerated.

In summary, the reaction described here represents a facile method for the preparation of substituted

oxindoles from readily accessible α-carbomethoxy-α-diazoacetanilides. It is mild, operationally simple and synthetically useful. Further work is in progress to delineate the scope and mechanism of this reaction.

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7. The structure of the oxindoles is readily inferred from their spectroscopic data: The infrared absorption of the carbonyl group occurrs in the range 1704–1713 cm^{-1}. In the ^{1}H nmr, the methylene protons at C-3 resonate as a singlet in the range δ 3.45–3.50 and, in the ^{13}C nmr, the C-3 signal appeared in the range δ 34.3–35.7.
8. A small amount of β-lactam was also isolated: Entry 3, 8%; Entry 10, 18%.
9. This is in analogy to the steric hindrance observed in the electrophilic aromatic substitution reactions of meta-disubstituted benzenes, see J. March, "Advanced Organic Chemistry," 4th ed., Wiley, New York, 1992, 514.

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