Transamination of Dimethylaminomethyleneoxindole

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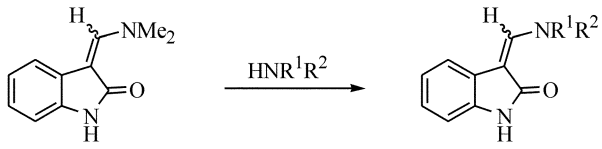
The oxindole skeleton has been found in numerous natural products and is also used as a synthetic intermediate for the preparation of numerous heterocyclic compounds with interesting biological property.[1] In particular, 3-methyleneoxindoles have been synthesized as GABAergic agents[2] enhance benzodiazepine binding and antagonize cyclic GMP elevations, and tyrosine kinase inhibitors[3] exhibit selectively toward different receptor tyrosine kinases. More recently, the biological importance of cyclin-dependent kinases as useful targets in cell cycle regulation has led to a considerable amount of synthetic works in oxindole-based compound.[4] Notwithstanding the importance of this heterocyclic system, existing methods for 3-substituted oxindole synthesis[5] are limited in their scope and generality.

As a part of our program, we have an interest in preparing 3-aminomethyleneoxindole derivatives for potential biological activity. There are many reports of 3-component condensation of active methylene compounds with several amine species, such as α-aminoacids, carbamates, and ureas, in the presence of triethyl orthoformate. They include cyclohexane-1,3-dione,[6] 4-hydroxy-1*H*-quinolin-2-one,[7] and 4-hydroxycoumarin.[8] It has offered an efficient method for introducing a wide variety of *exo*-aminomethylene moieties into the α-position of the active methylene compounds in a single step. Interestingly, it has been reported that oxindole undergoes a 3-component condensation with anilines and orthofomate.[9] The reaction proceeds smoothly with primary aliphatic and aromatic amines, whereas secondary amines give no or only low yields. While the impressive 3-component condensation has been made in the synthesis of 3-aminomethyleneoxindole derivatives, this is a need for the development of more flexible strategies that will accommodate a range of structural diversity.

In our search for general methods for preparing of 3-aminomethyleneoxindol derivatives, we turned our attention to more labile transamination precursors such as 3-dimethylaminomethyleneoxindole (**1**) and 3-ethoxymethyleneoxindole, which had been scantly investigated.[2,10] We observed that the transamination of **1** proceeded with secondary cyclic amines as well as primary amino group-containing substrates. Here, we would like to report the scope and generality of the transamination of **1** with the representative amine substrates,



1 **2-26**

Scheme 1

such as primary aliphatic and aromatic amines, α-aminoacids, hydrazines, and cyclic secondary amines. The transamination was conveniently carried out by refluxing a mixture of **1** with an appropriate amine in 2-propanol to give the functionalized 3-aminomethyleneoxindoles derivatives **2-26**, as shown in Scheme 1.

Our initial synthesis involved the preparation of **1** via the treatment of oxindole with dimethylformamide acetal in refluxing chloroform according to the literature procedure.[2,11] The simple treatment of aniline (entry 1) with **1** in refluxing 2-propanol gave **2** in 82% yield. With this promising result, we extended the transamination reaction to the readily available benzylamines (entries 2-3) and aliphatic amines (entries 4-5), as shown in Table 1. The yield was much better than that from the previously described 3-component condensation.[9] Next, the same reaction sequence was applied with different amino group-containing substrates, such as hydrazines and α-aminoesters. The reaction with the hydrazines (entries 6-9) underwent clean transformation into a new series of hydrazinomethyleneoxindole derivatives, but the reactions with carbamates and *N*-substituted ureas were not effective. When α-amino acids were used, no reaction was observed, presumably, due to the solubility problem. However, the reaction with α-amino esters (entries 10-17) proceeded into aminoester-incorporated oxindole derivatives. It is interesting to note that thiol and carboxyl group greatly affected the course of the reaction. When the esters of aspartic acid and cysteine were used, no products were observed.

The NMR spectra of the prepared 3-aminomethyleneoxindoles **2-18** in DMSO-d_6 displayed two set of signals around 9.4-8.9 ppm and 7.6-7.2 ppm, attributed to the C(3)-enamine proton. This is due to the existence of *Z*- and *E*-isomers, which were previously observed in many cases of 3-substituted oxindoles.[2,3,10] However, two isomeric forms could be distinguished by NOE analysis. The *Z*-isomer

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Table 1. Transamination of **1** with primary amino group-containing substrates

Entry	Amine	Time (h)	Product	Yield (%)
1	Aniline	20	**2**	82
2	Benzylamine	2	**3**	92
3	4-Methoxybenzylamine	20	**4**	85
4	Butylamine	20	**5**	68
5	3-Amino-1-propanol	20	**6**	62
6	Hydrazine hydrate	1	**7**	60
7	Methylhydrazine	1	**8**	53
8	Phenylhydrazine	1	**9**	86
9	2-Hydrazinopyridine	20	**10**	67
10	Glycine ethyl ester	23	**11**	80
11	Valine methyl ester	22	**12**	88
12	Serine ethyl ester	20	**13**	33
13	Methionine ethyl ester	20	**14**	85
14	Phenylalanine methyl ester	6	**15**	89
15	Tyrosine methyl ester	23	**16**	94
16	Histidine methyl ester	22	**17**	84
17	Tryptophan methyl ester	20	**18**	94

shows NOE effect between the C(3)-vinyl proton and C(4)-aromatic proton, whereas the *E*-isomer does not show NOE enhancement. Most of 3-aminomethyleneoxindoles derivatives appear to favor the *Z*-isomers (*Z*/*E* = 3-6/1) in DMSO-d_6. The difference in the chemical shift was interpreted that a hydrogen-bonding capability to the C(2)-carbonyl group pretty much contributes to the low field shift of the C(3)-enamine proton in *Z*-isomer.[12] Thus, one possible explanation is that the preference of the *Z*-isomer arises from its involvement of the intramolecular hydrogen-bonding.

It has been reported that the 3-component condensation of oxindole with the secondary amines and orthoformate give no or only low yields. Thus, in order to examine the scope of the transamination of **1**, we varied the amine substrate with *N*-containing heterocyclic amines. The same reaction sequence applied, and the products from pyrrolidine, piperidine, morpholine, and piperazine were obtained in good yields (Table 2). But the reactions with aromatic amines, such as pyrrole, imidazole, and indole, were not effective. Contrasting to the compounds **2-18**, the products **19-26** appear to favor the *E*-isomers (*E*/*Z* = 2-3/1) in DMSO-d_6. This may be due to the steric interference between the C(2)-carbonyl group and the bulky C(3)-substituents in their *Z*-isomeric forms.

Table 2. Transamination of **1** with cyclic secondary amines

Entry	Amine	Time (h)	Product	Yield (%)
1	Pyrrolidine	25	**19**	55
2	Piperidine	9	**20**	89
3	Morpholine	9	**21**	73
4	1-Methylpiperazine	24	**22**	95
5	Phenylpiperazine	26	**23**	89
6	1-Piperonylpiperazine	26	**24**	90
7	Acetylpiperazine	24	**25**	78
8	1-(2-Hydroxyethyl)piperazine	24	**26**	82

In summary, an efficient synthesis of 3-aminomethyleneoxindole derivatives **2-26** has been achieved by the transamination of 3-dimethylaminomethyleneoxindole **1** with several amine substrates in refluxing 2-propanol. The reaction allowed the transamination of **1** with not only primary amines but also cyclic secondary amines.[13] It is noteworthy that the transamination with the cyclic secondary amines proceeded to afford a new series of methyleneoxindole derivatives, which were previously difficult to obtain.

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13. General procedure for the transamination (Table 2, entry 1): A mixture of **1** (188 mg, 1.0 mmole) and pyrrolidine (213 mg, 3.0 mmole) in 2-propanol (5 mL) was stirred at 95-100 °C for 25 hr. The precipitate was filtered by suction while on cooling to room temperature, and washed with 2-propanol, and then re-crystallized from chloroform/ hexane to give 117 mg (55%) of **19** as a solid: mp 195-196 °C; EIMS *m/z* (rel intensity) 214 (M^+, 72), 185 (15), 158 (13), 144 (43), 130 (30), 117 (81), 89 (41), 70 (100), 41 (95); ^{1}H NMR (DMSO-d_6) δ 9.99 and 9.86 (s, NH(1)), 7.72 and 7.52 (s, CH(3)), 7.50 and 7.23 (d, 1H(4), J = 7.2 Hz), 6.93-6.67 (m, 3H), 3.94-3.68 (m, 4H), 1.96-1.91 (m, 4H); Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.96; H, 6.61; N, 13.02%.