A Novel Procedure for the Formation of Isatins *via* Carbonylation of Lithiated *N'*-Aryl-*N*,*N*-dimethylureas

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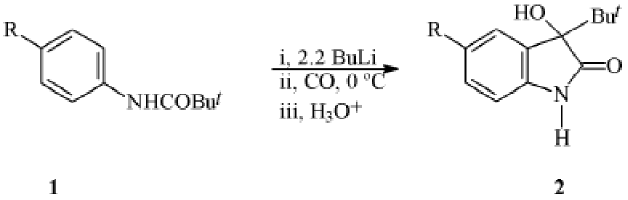
Abstract: Isatin and substituted isatins can be formed in very good yields from the appropriate *N'*-(2-bromoaryl)-*N*,*N*-dimethylureas *via* bromine-lithium exchange followed by treatment with carbon monoxide.

Key words: carbonylation, isatins, lithiation, ureas, organolithiums

Although organolithium compounds are frequently reacted with carbon dioxide for the formation of carboxylic acids, reactions with carbon monoxide are much more limited due to the extreme reactivity of the acyllithium intermediate. This reactivity leads to dimerization, decomposition, reaction with further carbon monoxide or other reactions, giving rise to a range of compounds other than those expected from simple electrophilic trapping.[1]

A range of acyl anion equivalents has been developed to overcome this problem,[2] but such reagents are not without drawbacks. In particular they require additional steps to unmask the carbonyl functionality and they cannot be used for introducing isotopically labelled carbon monoxide. It has been shown by Seyferth *et al.* that it is possible to trap acyllithiums derived from carbonylation of alkyllithium reagents given that the reaction is carried out at very low temperature (typically -130 ºC).[3] The conditions are, however, rather restrictive and the method has only rarely been used with aryllithiums.[4] Therefore, it appeared that intramolecular trapping of acyllithiums might provide a more generally useful synthetic approach for carbonylation reactions of organolithium reagents.[5]

Early attempts at this approach in our laboratory led to successful carbonylation of doubly lithiated *N*-pivaloylanilines (**1**) and the synthesis of 3-*tert*-butyldioxindoles (**2**) in good yields (Scheme 1).[6] The reaction involves a cascade of reactions comprising carbonylation of the original organolithium reagent, cyclisation of the acyllithium onto the pivaloylamino group, and then rearrangement to give the final intermediate, followed by protonation during workup.

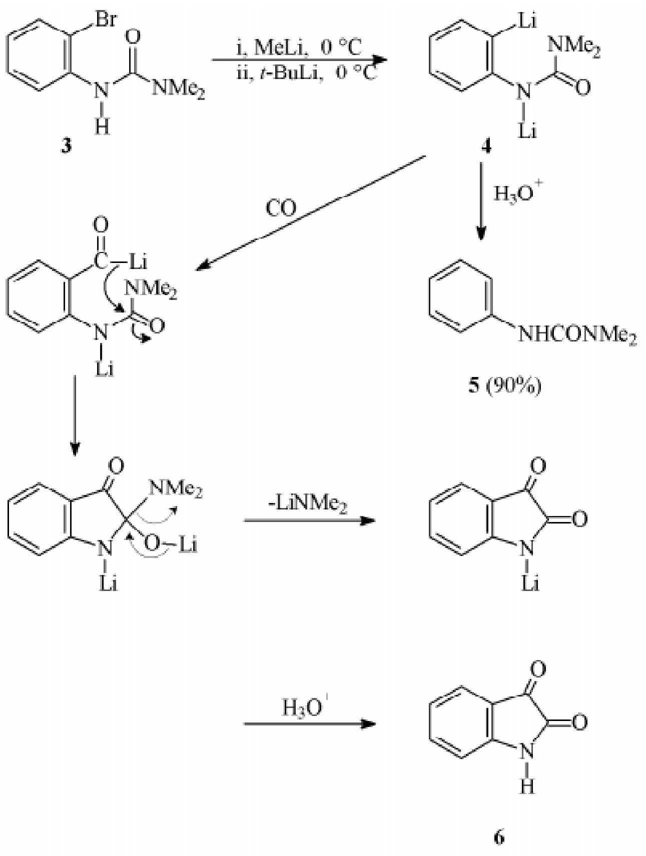


Scheme 1

The method has particular potential for the synthesis of isotopically labelled indole compounds because carbon monoxide, the source of the additional ring carbon atom, is easily obtainable in all isotopic forms. Even ^{11}CO, with a half-life of only 22 minutes, is easily generated, which gives the reaction potential for use in positron emission tomography (PET), a non-invasive medical imaging technique which requires the synthesis of biologically-active compounds labelled with short-lived radioisotopes.[7] Unfortunately, the presence of a *tert*-butyl group in compounds **2** greatly restricts the utility of those compounds. We have therefore sought to replace the pivaloyl group in the starting material with another group that would provide products of greater utility. We now report on the successful generation of isatins from *N'*-(2-bromoaryl)-*N*,*N*-dimethylureas.

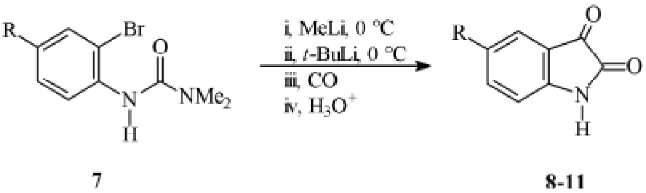
Initially we tried the reaction of carbon monoxide and doubly lithiated *N*-*tert*-butoxycarbonylaniline, (PhNHCO$_2$Bu^t),[8] but although the reaction mixture turned a deep colour on introduction of carbon monoxide, as had been the case with doubly lithiated *N*-pivaloylaniline, we were unable to isolate indole derivatives in more than trace amounts after work-up of the reaction mixture.

We had more success with doubly lithiated *N'*-aryl-*N*,*N*-dimethylthioureas, which on carbonylation led to indigotins,[9] but these products are also not very amenable to further modification. We therefore turned our attention to doubly lithiated *N'*-aryl-*N*,*N*-dimethylureas. Because of our own interest in the use of doubly lithiated species and related compounds for organic synthesis[10] we attempted the direct double lithiation of *N*,*N*-dimethyl-*N'*-phenylurea but could not achieve successful *ortho*-lithiation in any conditions we tried. Fortunately, this difficulty was easily overcome by the use of *N'*-(2-bromophenyl)-*N*,*N*-dimethylurea (**3**) which successfully underwent lithiation on nitrogen to form the monolithio reagent using MeLi, followed by bromine-lithium exchange using *t*-BuLi to give the dilithio reagent **4**. To test the extent to which the dilithio reagent **4** had formed, it was protonated using saturated ammonium chloride solution to give *N*,*N*-dimethyl-*N'*-phenylurea (**5**) in 90% isolated yield (Scheme 2). The dilithio reagent **4** thus formed was then exposed to carbon monoxide. The mixture turned a deep colour and after work-up isatin was obtained. A series of experiments was conducted in which the reaction conditions were varied in an attempt to optimise the yield. Indeed, when a solution of compound **3** in THF at 0 °C was treated with MeLi (1.05 equiv.) and then *t*-BuLi (2.1 equiv.), followed by reaction of the dilithio reagent **4** thus obtained with carbon monoxide, isatin (**6**) was obtained in 76% isolated yield.[11] The likely mechanism, involving carbonylation followed by cyclisation, is shown in Scheme 2.



Scheme 2

Isatin is a useful synthetic intermediate. It reacts with carbanions to give 3-substituted dioxindoles.[12] Therefore, the reaction was applied to a range of *N*'-(2-bromoaryl)-*N*,*N*-dimethylureas (**7**) to afford substituted isatins **8-11** (Scheme 3) in very good yields (Table 1).[11]



Scheme 3

Table 1 Yields of substituted isatins

Product	R	Yield (%)[a]	Mp (°C)
6	H	76	201-202 (dec.) (lit.,[13] 200-202)
8	Cl	77	250-252 (lit.,[13] 249-252)
9	Me	72	186-187 (lit.,[13] 185-187)
10[14]	^{i}Pr	71	140
11	F	79	223 (lit.,[15] 223)

[a] Yields of isolated purified product.

As can be seen from Table 1, the yields are good, and the reaction accommodates a range of substitutents in the isatin moiety. Therefore, it represents a useful new procedure for the formation of isatins. This work extends the applicability of our work on the tandem carbonylation-intramolecular trapping of acyllithiums and is more generally useful than the reaction of doubly lithiated pivaloylanilines, the final product having no bulky *tert*-butyl group and being much more amenable to modification. It should prove more attractive for synthesis of compounds of interest for positron emission tomography.

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References and Notes

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(11) **Typical Experimental Procedure:** *Formation of substituted isatins.* To a cooled solution (0 ºC) of the appropriate *N'*-(2-bromoaryl)-*N*,*N*-dimethylurea (2.0 mmol) in dry THF (15 ml) under a nitrogen atmosphere was added a solution of methyllithium (2.1 ml, 1.0 M, 2.1 mmol) in tetrahydrofuran, in order to deprotonate the nitrogen. Bromine-lithium exchange was then effected by the addition of a solution of *t*-butyllithium, (2.47 ml, 1.7 M, 4.2 mmol) in heptane. The mixture was stirred at 0 ºC for 1 h then exposed to carbon monoxide, which was introduced to the reaction vessel from a balloon fitted with a needle, *via* a septum. The dilithio reagent was stirred under carbon monoxide for 30 min, after which, the mixture was diluted with ethyl acetate (10 ml) and then quenched with aqueous saturated ammonium chloride solution (10 ml). The organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product obtained was purified by flash column chromatography using a 50/50 mixture of diethyl ether and light petroleum (bp 30-40 ºC) to give the pure isatin. The yields obtained are recorded in Table 1.

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(14) **10**: IR (KBr) 3350, 1750, 1620, 1520, 1430, 1220, 1150, 1045, 1040, 850, 770 and 705 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.95 (1 H, s, exch.), 7.47 (1 H, dd, J = 1.4 & 8.0 Hz), 7.37 (1 H, d, J = 1.4 Hz), 6.83 (1 H, d, J = 8.0 Hz), 2.86 (1 H, septet, J = 6.9 Hz), 1.16 (6 H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 184.62 (s), 159.56 (s), 148.91 (s), 143.16 (d), 136.57 (s), 122.26 (d), 117.84 (s), 112.13 (d), 32.75 (d), 23.72 (q); *m/z* (EI), 189 (M$^+$, 25%), 161 (53), 146 (100), 91 (76), 63 (50), 41 (53) and 39 (78); *m/z* (CI), 207 (M$^+$ + NH$_4$, 100%), 190 (MH$^+$, 8), 176 (37), 160 (57), 136 (17) and 77 (12); HREIMS: found *m/z* 189.0790 (M$^+$); calcd for $C_{11}H_{11}NO_2$ 189.0789).

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