JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2006; **49**: 615–622.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.1067

Research Article

Two robust, efficient syntheses of [*phenyl ring*-U-^{14}C]indole through use of [*phenyl ring*-U-^{14}C]aniline

Carrie A. B. Wager* and Sandra A. Miller
Chemical Research and Development, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, USA

Summary

Two robust, efficient syntheses of [*phenyl ring*-U-^{14}C]indole are presented. In the first synthesis, we developed optimum reaction conditions for the Houben–Hoesch alkylation of chloro acetonitrile with aniline. This was found through the screening of several Lewis acids coupled with the use of Sugasawa conditions for ortho direction. Following alkylation, the resultant imine was hydrolyzed to the phenone, and then thermal cyclization followed by reduction led to indole. In the second synthesis of [*phenyl ring*-U-^{14}C]indole, we utilized microwave-enhanced conditions for the key coupling. In this transformation, aniline was alkylated with the acetal of bromo acetaldehyde. The mono-alkylated aniline was then transformed in a straightforward manner to indole. Copyright © 2006 John Wiley & Sons, Ltd.

Received 12 October 2005; Revised 5 March 2006; Accepted 6 March 2006

Key Words: indole; Houben–Hoesch; directed acylation; aniline; microwave

Introduction

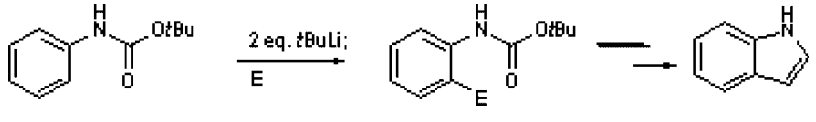
Heterocycle synthesis is a cornerstone in the synthesis of isotopically labelled compounds. This is due to the fact that a majority of labelled compounds are built as radiotracers for adsorption, distribution, metabolism and excretion (ADME) studies, where it is critical that label placement be located in a metabolically stable position.[1] The indole ring is present in many pharmaceutically active compounds,[2] and recently, in the course of our work, it became necessary to synthesize an isotopically labelled indole core and incorporate it in a drug candidate being pursued for development.

*Correspondence to: Carrie A. B. Wager, Chemical Research and Development, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, USA. E-mail: carrie.b.wager@pfizer.com

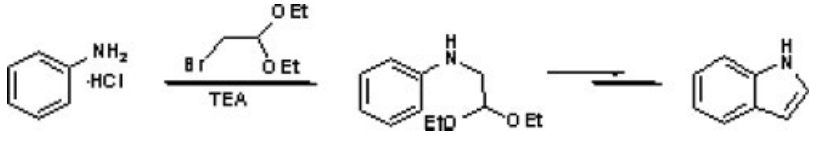
Labelled [*phenyl ring*-U-^{14}C]aniline is relatively inexpensive and by nature the radiolabelled components are encapsulated in a metabolically stable aromatic ring. These two features are critical when faced with a multi-step synthesis to the targeted candidate, because more than a few milliCuries of activity are necessary to carry the synthesis to completion. Therefore, our research focused on aniline as our primary building block for the synthesis of unsubstituted indole.

Of the few known options for the synthesis of labelled indole, one synthesis involves directed lithiation of acylated aniline (Scheme 1).[3] This method was not amenable to the small scale we were working on, due to variable results based on the need to keep the system rigorously anhydrous. The second method is an alkylation of the aniline and then cyclization of the resultant secondary amine to indole (Scheme 2).[4] Because the yield of our initial alkylation of aniline was poor, we set aside this synthetic approach to focus on the ortho-directed acylation approach (Scheme 3). However, the attractive and straightforward nature of the alkylation route was worthy of further consideration.

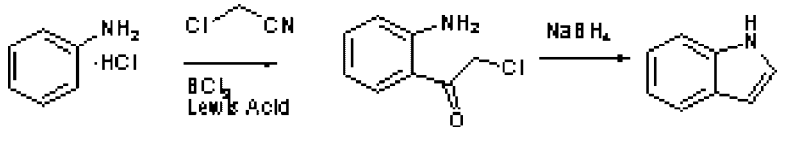
When an isotope literature search failed to provide a robust and efficient route, we returned to search for non-labelled options. Most syntheses require substituted anilines or produce substituted indole products, e.g. the Fisher indole synthesis. In unsubstituted cases early references for indole synthesis



Scheme 1.



Scheme 2.



Scheme 3.

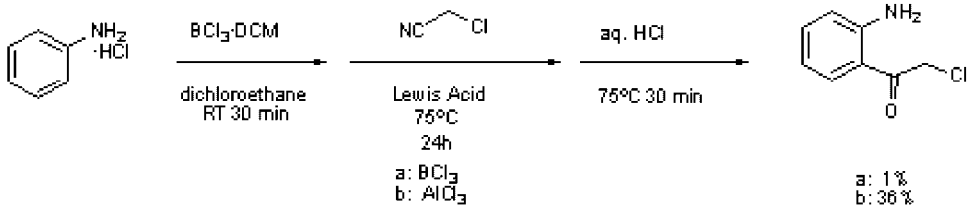
DOI: 10.1002/jlcr

utilize Friedel–Crafts or Houben–Hoesch chemistry which use either acyl or nitrile electrophiles, respectively.[5] These methods lacked regioselectivity and therefore the yield of the desired product was moderate and required difficult separations. Sugasawa overcame the issue of regioselectivity, through the use of a boron tether to give exclusive alpha substitution.[6] This regioselectivity was a big improvement over existing syntheses, however, yields were moderate warranting further research. Some investigators extended this method through the use of boron coordination and additional Lewis acids.[7] These served as our starting point. As the majority of these systems were stacked in favor of electrophilic aromatic substitution having electron-rich substrates, they were not ideal for our substrate, aniline, which is only weakly electron rich. We chose to optimize this reaction chemistry through the use of additional Lewis acids. We decided that we would take advantage of the Sugasawa method for ortho direction, and develop optimal conditions for aniline that would boost reaction rate and yield. We focused our efforts on screening various Lewis acids to accomplish our goal (increased reaction rate and improved yields.) The work described herein was performed with cold or stable labelled reagents.

Discussion

The first pivotal experiments included Sugasawa conditions for ortho direction and (1) use of an additional amount of boron trichloride as the Lewis acid and (2) use of aluminum trichloride as an additional Lewis acid. Results with extra boron trichloride were not promising. We achieved at best only a 3% yield. The use of an additive (aluminum trichloride) was much more promising. We were able to achieve the desired acylated product in a moderate 36% yield (Scheme 4). Although a moderate yield, we believed it to be a promising start and therefore initiated screening of various Lewis acids using an Argonaut AS2410 parallel reaction workstation.

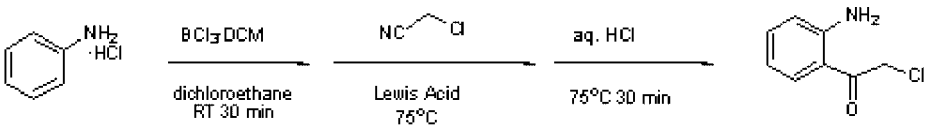
Our decision to use aluminum, antimony, titanium, iron and zinc as Lewis acids came from perusal of the Houben–Hoesch and Friedel–Crafts literature. Upon screening various Lewis acids, two clearly came out on top of the rest:



Scheme 4.

DOI: 10.1002/jlcr

Table 1. Various Lewis Acid Additives with the Houben-Hoesch Acylation of Aniline



Time vs. Lewis Acid	$AlCl_3$	$SbCl_5$	$TiCl_4$	$FeCl_3$	$ZnCl_2$	BCl_3
1 h	ND	ND*	5%	ND*	2%	<1%
3 h	37%	ND*	17%	ND*	12%	4%
24h	36%	5%	49%	19.0%	79%	<1%

* isolated mass balance was made up of a majority of byproducts and not starting aniline

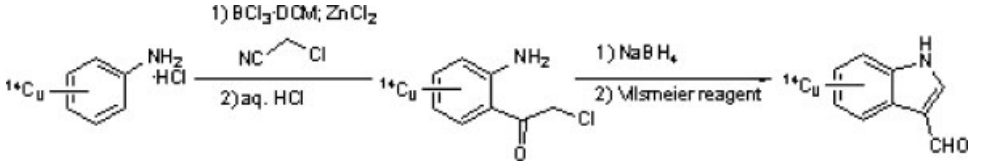
titanium tetrachloride and zinc dichloride (Table 1). Both reactions gave moderate to good yields of the isolated desired product.

Clearly, additional equivalents of the same Lewis acid (i.e. additional boron trichloride) were not beneficial in our hands. This could be due to several factors, one being the formation of borate complexes that just do not respond in these reaction conditions. Interestingly, both antimony and iron gave low amounts of the desired product and a significant amount of by-products. Antimony pentachloride was chosen due to its strong Lewis acid character. It is known that antimony pentachloride can be beneficial even in weakly electron-rich systems.[8] However, it is also known that this Lewis acid can produce nitrile homo-coupled products[5b]. Initial results with titanium tetrachloride looked promising, however, this reaction was slower than we would like. Historically, both aluminum and zinc have been used in Houben–Hoesch chemistry: the original Gatterman reaction with cyanic acid used aluminum trichloride and the initial report of trapping alkyl nitriles by Hoesch occurred with the aid of zinc dichloride. Even though aluminum trichloride started to look promising, this reaction stalled after a few hours. Nonetheless, we were very excited to find the addition of zinc dichloride gave the desired product in excellent yield (79%). In the case of zinc, both its Lewis acid and dehydrating properties are mutually beneficial here.

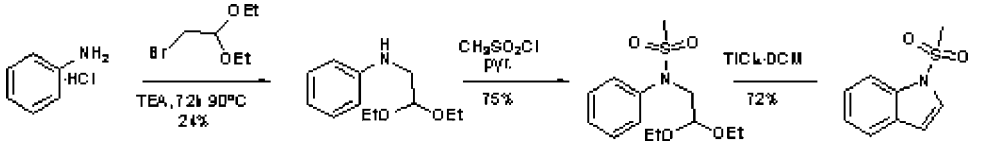
The optimal conditions described above were applied to the synthesis of both the [*phenyl ring*-U-^{14}C]indole and then the [*phenyl ring*-U-^{14}C]-indole-3-carboxaldehyde, see Scheme 5. A representative 'Experimental' section is presented at the end of this article. The use of inexpensive [*phenyl ring*-U-^{14}C]aniline hydrochloride and optimal conditions afforded two isotopically labelled indole compounds in good yield.

The attractive and straightforward nature of the alkylation route to unsubstituted indole was revisited with the idea of improving the initial

DOI: 10.1002/jlcr

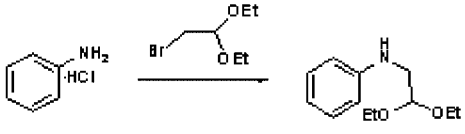


Scheme 5.



Scheme 6.

Table 2. Optimization on the Alkylation of Aniline



Rxn	Solvent	Base	Time (h)	Temp (°C)	MW?	Product
1	95% EtOH/water	triethyl amine	72	90	N	24%
2	95% EtOH/water	triethyl amine	0.5	180	Y	55%
3	95% EtOH/tetrahydrofuran	$NaHCO_3$	72	83	N	50%
4	95% EtOH/water	$NaHCO_3$	0.5	180	Y	66%
5	tetrahydrofuran	NaHMDS	3	25	N	69%

alkylation step (Scheme 6). This route is promising with the exception of the first step in the transformation. With extended reaction times and elevated temperature, we saw this alkylation step as a perfect candidate for microwave conditions. As seen in Table 2, initial reaction conditions (Reaction 1) show 24% product after 3 days. Without changing the reaction components at all, however, employing the microwave we were able to achieve a much better yield, 55%, and drop the reaction time to 0.5 h (Table 2, Reaction 2). Switching to an inorganic base, sodium bicarbonate under thermal conditions, we saw improvement on the amount of isolated desired product, although still requiring a 3 day (Reaction 3). Again, with utilization of microwave technology, we were able to drop the reaction time from 3 days to half an

DOI: 10.1002/jlcr

hour with a further improvement in the isolated yield of the desired product. Finally, one last variation on base, sodium hexamethyldisilazide, (Reaction 5, Table 2) resulted in desired product in 69% yield. In summary, there are two sets of reaction conditions that are optimized: use of sodium bicarbonate as base with the microwave instrument and use of sodium hexamethyldisilazide using conventional thermal conditions. Consequently, depending on what ability is available, then reaction conditions can be chosen accordingly.

Conclusion

Through use of microwave, parallel, and conventional reaction technology, we have been able to evaluate and determine two robust and efficient systems for the synthesis of labelled indole. By utilizing a microwave, we have been able to optimize a route to indole. This route relies on the alkylation of aniline with the acetal of bromo acetaldehyde. After screening various Lewis acids, we have found the use of zinc dichloride in addition to boron trichloride allows for the efficient trapping of chloro acetonitrile by aniline. These reactions are amenable to small or large scale and are not dependant on an anhydrous or rigorously inert atmosphere. Both reactions have been optimized to possess a straightforward reaction processing, by nature of a very clean reaction profile. We took advantage of an excess of inexpensive reagents, chloro acetonitrile and the acetal of bromo acetaldehyde. These easily accessible reagents were coupled with a relatively inexpensive and metabolically stable label position in aniline. Additional experiments are ongoing in our laboratory to further elucidate these reaction sequences.

Experimental

[phenyl ring-U-^{14}C]-1-(2-aminophenyl)-2-chloroethanone

[*phenyl ring*-U-^{14}C]Aniline hydrochloride (200 mCi, 1.6 mmol, source: GE Biosciences) was suspended in dichloroethane (10 ml) under a nitrogen atmosphere. Boron trichloride in dichloromethane (5.2 ml, 5.2 mmol) was added dropwise at room temperature. The mixture was stirred until the reaction was homogeneous. Chloro acetonitrile (350 µl, 5.5 mmol) was added, followed by zinc dichloride (870 mg, 6.4 mmol). The now heterogeneous mixture was stirred at 75°C for 22 h. After cooling, 1 N hydrochloric acid (10 ml, 10 mmol) was added and a yellow precipitate was formed. The mixture was warmed to 75°C for 1 h to ensure ketamine hydrolysis. The reaction was then cooled to room temperature and the aqueous solution was extracted with dichloromethane (5×10 ml), the organics were dried ($MgSO_4$), and concentrated to give 130 mCi of the crude product. TLC (100% dichloromethane) showed the desired product to be 92% radiochemically pure ($R_f = 0.6$)(Bioscan). Silica gel chromatography gave 122 mCi of [*phenyl ring*-U-^{14}C]-

DOI: 10.1002/jlcr

1-(2-aminophenyl)-2-chloroethanone, 97% radiochemical purity (HPLC), GCMS gave mass units of 169 m/z (unlabelled) and 183 m/z (six labels).

[phenyl ring-U-^{14}C]-Indole

To a stirred solution of [*phenyl ring*-U-^{14}C]-1-(2-aminophenyl)-2-chloroethanone, (122 mCi, 0.98 mmol) in dioxane (5 ml) containing water (0.5 ml) was added sodium borohydride (34 mg, 0.90 mmol). The solution was held at reflux for 17 h. After removal of solvent, the reaction was partitioned between dichloromethane and water. The aqueous layer was extracted (5 × 10 ml) with dichloromethane. The organics were dried ($MgSO_4$) and concentrated to give 110 mCi of crude product, 81% radiochemically pure by HPLC. Silica gel chromatography (10% ethyl acetate/hexanes) gave 85 mCi of the desired [*phenyl ring*-U-^{14}C]-indole, > 99% radiochemically pure (HPLC). GCMS gave masses of 117 m/z (unlabelled) and 131 m/z (six labels).

[phenyl ring-U-^{14}C]-Indole-3-carboxaldehyde

[*phenyl ring*-U-^{14}C]-indole (85 mCi, 0.68 mmol) was dissolved in dimethylformamide (200 µl) under a nitrogen atmosphere. In a separate tear-shaped flask under a nitrogen atmosphere, 340 µl of dimethylformamide was cooled to 0°C, and then phosphorous oxychloride (100 µl, 1.1 mmol) was added. The presumed Vilsmeier–Haack solution was syringed into the reaction flask containing the aforementioned [*phenyl ring*-U-^{14}C]-indole solution. The resulting reaction mixture was then heated to 35°C for 1 h, resulting in a tan-colored precipitate. Water (500 µl) was added to the mixture to dissolve the solids, followed by 4.8 N NaOH, (300 µl) dropwise, and then an additional amount (700 µl) at once. This brown, clear liquid was then heated to reflux for 5 min. After cooling the reaction was extracted with ethyl acetate (5 × 10 ml) and the organics dried ($MgSO_4$), filtered, and concentrated to give 75 mCi of crude product, 87% radiochemically pure (HPLC). Silica gel chromatography (10% ethyl acetate/hexanes) gave 59 mCi of [*phenyl ring*-U-^{14}C]-indole-3-carboxaldehyde > 99% radiochemically pure by HPLC. GCMS gave mass units of 144 m/z (unlabelled) and 158 m/z (six labels).

N-(2,2-Diethoxyethyl)benzenamine

Aniline hydrochloride (125 mg, 0.97 mmol) was suspended in 95% ethanol/water (3 ml) in a microwave safe 2.5 ml glass vial with magnetic stir bar. Triethylamine (400 µl, 2.9 mmol) was added, followed by 2-bromo-1, 1-diethoxyethane (180 µl, 1.2 mmol). The vial was sealed and placed in a Biotage Initiator® 8 microwave instrument. The reaction was stirred for 10 s, followed by irradiation at high absorption to a temperature of 180°C for 30 min. After cooling, the reaction was concentrated and partitioned between

DOI: 10.1002/jlcr

ethyl acetate (10 ml) and water (10 ml). The aqueous was extracted with ethyl acetate (3×10 ml), the organics were dried ($MgSO_4$), and concentrated to give the crude oil (316 mg). Silica gel chromatography (10% ethyl acetate/hexanes) gave *N*-(2,2-diethoxyethyl)benzenamine (113 mg, 56% yield).

N-(2,2-Diethoxyethyl)benzenamine

Aniline (410 µl, 4.5 mmol) was dissolved in tetrahydrofuran (20 ml). One molar sodium hexamethydisylazide in tetrahydrofuran (4.5 ml, 4.5 mmol) was added dropwise. After stirring at room temperature for 2 h, 2-bromo-1,1-diethoxyethane (810 µl, 5.4 mmol) was added dropwise. The reaction was allowed to stir for 12 h. The reaction was concentrated and partitioned between ethyl acetate (20 ml) and water (20 ml). The organic was dried ($MgSO_4$), and concentrated to give a crude oil (1.42 g). Silica gel chromatography (10% ethyl acetate/hexanes) gave *N*-(2,2-diethoxyethyl)benzenamine (651 mg, 69% yield).

References

1. McCarthy KE. *Curr Pharm Des* 2000; **6**: 1057–1083.
2. (a) Müller G. *Drug Discovery Today* 2003; **8**: 681–691; (b) DeSimone RW, Currie KS, Mitchell SA, Darrow JW, Pippin DA. *Comb Chem High Throughput Screening* 2004; **7**: 473–493.
3. (a) Muchowski JM, Venuti MC. *J Org Chem* 1980; **45**: 4798–4801; (b) Dischino DD, Gribkoff VK, Hewawasam P, Luke GM, Rinehart JK, Spears TL, Starrett Jr JE. *J Label Compd Radiopharm* 2003; **46**: 139–149.
4. Ilic N, Cohen JD. *J Label Compd Radiopharm* 2004; **47**: 635–646.
5. (a) Hoesch K. *Ber* 1915; **48**: 1122; (b) Houben J. *Ber* 1926; **59**: 2878; (c) Ruske W. *Friedel-Crafts and Related Reactions*, vol. III (Part 1), Olah GA (ed.). Interscience: New York, 1964; 407; (d) Friedel C, Crafts JM. *CR* 1877; **84**: 1450; (e) Olah GA, Cupas CA. *Kirk-Othmer Encyclopedia of Chemical Technology* (2nd edn), vol. 10. Wiley Interscience: New York, 1966; 135–166; (f) Mahato SB. *J Indian Chem Soc* 2000; **77**: 175–191.
6. Sugasawa T. *Stud Org Chem* (Amsterdam) 1986; **25**: 63–79 and references therein.
7. (a) Sugasawa T, Adachi M, Sasakura K, Kitagawa A. *J Org Chem* 1979; **44**: 578–586; (b) Nimtz M, Haefelinger G. *Liebigs Ann Chem* 1987; 765–770.
8. Yakobson GG, Furin GG. *Synthesis* 1980; **5**: 345–364.

DOI: 10.1002/jlcr