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9-Phenylfluorene: a powerful labeling agent

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Abstract—A highly efficient method for labeling with deuterium is described using an acidic hydrocarbon as transfer agent. Using 9-[^2H]-9-phenylfluorene as the deuterium donor, numerous organic compounds have been labeled in fair yields and good isotopic enrichment.

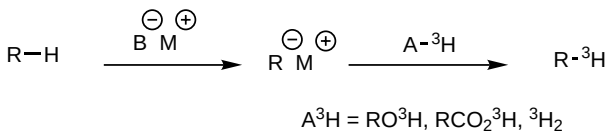
In recent decades, increasing use has been made of tritiated compounds in biological evaluations, mainly of metabolism. This use is limited by the difficulty of obtaining tritiated molecules of high specific activity, mainly because of the hazards of manipulating radioactive materials. Three standard methods are used to prepare tritiated compounds of high specific activity. The first method consists of catalytic reductions, halogen/tritium exchange or hydride reductions[1] of a suitable precursor. This approach requires prior synthesis of the derivative, and is labor-intensive. Furthermore, tritium gas is involved and all reactions must carried out in a specialized laboratory equipped with glove boxes and radioactivity hazard evaluation. All these drawbacks seriously limit the scope of this methodology. The second method takes advantage of isotopic exchange using either $^3H_2$ gas and a transition metal derivative[2] or catalyzed by acids[3] or bases.[4] In the third method, an anion is generated by metallation of the target substrate, which is then quenched with tritiated water,[5] acids[6] or even tritium gas[7] (Scheme 1).

In the second and third methods, no synthesis of derivatives is required, but only authorized laboratories are able to run these experiments since $^3H_2$ gas is used to obtain quenching agents of high specific activity.

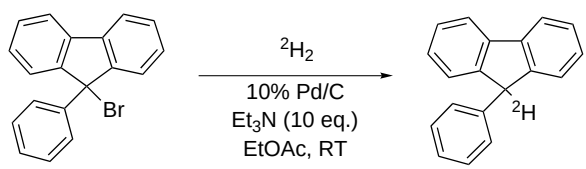
In this paper, we introduce a new approach that has the advantage of the third method (no need for prior derivatization of the substrate to be labeled) with none of the previously mentioned drawbacks (no use of an expensive catalyst, no handling of $^3H_2$ gas or ^3H_2O).

Our aim has been to design a general, environmentally friendly and safe method, based on the same acid–base concept (Scheme 1). We needed to find a labeled 'water substitute' that was easy to prepare at high isotopic enrichment, easy to handle (at least non-volatile), efficiently transferable to the isotope, easy to remove from a reaction mixture, and with a pK_a far removed from 14 to avoid rapid exchange with water and resulting isotopic dilution. Surprisingly, few research groups have explored the usefulness of labeled acidic hydrocarbons for such purposes.[8] Extensive literature searches revealed that 9-phenylfluorene (9-PhFl) best fitted the above-mentioned requirements, with a pK_a value of 17.9 in DMSO.[9]

The first step was to rationalize an efficient synthesis of 9-[^2H]-9-phenylfluorene keeping in mind that this route has to be transposable to the tritium analogue. Starting from 9-bromo-9-phenylfluorene, classical hydrogenoly-



Scheme 1.



Scheme 2.

Keywords: acidic hydrocarbons; anions; deuterium; labeling.

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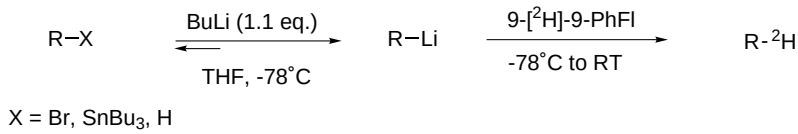
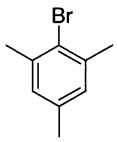
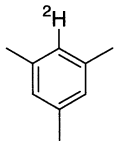
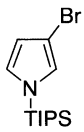
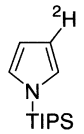
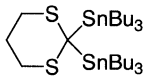
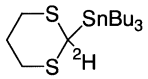
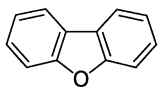
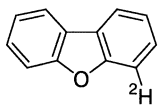
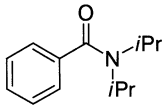
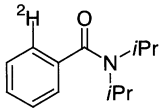
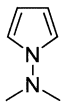
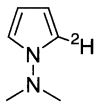
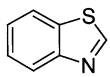
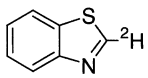
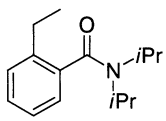
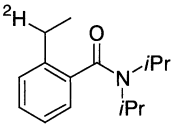
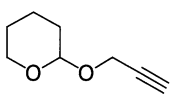
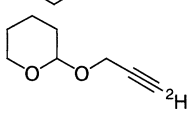
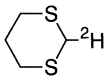
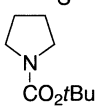
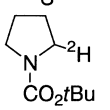
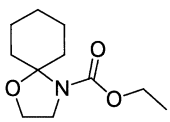
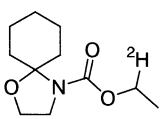


Scheme 3.

Table 1. Labeling experiments using 9-[^2H]-9-PhFl

Entry	Substrate	Product	Yield (%)	i.e. (%)[11]
1			89	100
2			68	91
3			82	91
4			88	82
5			90	100
6			70	70
7			50	78
8			65	94
9			63	79
10			96	100
11			61	70
12			77	96

sis of the carbon–bromide bond under $^2H_2$ in the presence of a catalytic amount of Pd^0 gave the expected 9-[^2H]-9-PhFl in yields ranging from 82 to 95%, and isotopic enrichment up to 98.5% on a 0.3–5 g scale (Scheme 2). The isotopic enrichment of 9-[^2H]-9-PhFl was improved considerably (from 91 to 98.5%) by washing the catalyst with $^2H_2$ prior to the reduction step.[10]

We then investigated the label-transfer potential of this compound, starting first from halogeno or stannyl

derivatives to eliminate the risk of a partial metallation step (Scheme 3).

As shown in Table 1 (entries 1–3), the method is highly efficient (isotopic enrichment up to 100%). In terms of our initial aim (no synthetic derivative needed) it is simple to start from the target compound, abstract a proton regioselectively and replace it by its isotope (entries 5–12). The methodology is quite powerful and general since aromatic (entries 4–7), benzylic (entry 8), acetylenic (entry 9) and aliphatic positions (entries 10–12) have been labeled.

In conclusion, this methodology seems very promising because of its general applicability (access to a wide range of labeled compounds in a regiospecific fashion). The only limitation is the metallation process which requires acidic protons with a pK_a above 18. Due to the easy deuterodehalogenation of 9-bromo-9-phenylfluorene, this approach should be easily transposable to tritium. This should enable most standard chemistry laboratories to synthesize tritiated molecules simply and safely.

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11. Deuterium incorporation was measured by integration of the respective ^{1}H NMR signals and by referring to the signal of another proton or group of protons within the molecule as internal standard. ^{1}H Spectra of labeled compounds were in full agreement with those of the starting materials.