**t-BuOK-catalysed alkylation of fluorene with alcohols: a highly green route to 9-monoalkylfluorene derivatives†**

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A simple, mild and efficient protocol was developed for the alkylation of fluorene with alcohols in the presence of t-BuOK as catalyst, affording the desired 9-monoalkylfluorenes with near quantitative yields in most cases.

Herein, we wish to report a green protocol for t-BuOK-catalysed 9-alkylation of fluorene with alcohols.

**Results and discussion**

This work was initiated by some new recognitions from our own studies on alcohol activation termed as the “borrowing hydrogen” reaction:6 upon following a base-promoted reaction of fluorene and an aliphatic alcohol, we found that both the type and the quantity of bases dramatically affected reaction conditions, conversions, as well as product distributions, and interestingly the alkylated product increased with reducing the amount of the base, contrary to what we usually believed.

Then, a more detailed survey of the base-catalysed alkylation reaction was performed by choosing fluorene and p-methoxybenzyl alcohol as model substrates, and the results are summarized in Table 1. After some experimentation, our standard reaction conditions ([i.e., in the presence of 50 mol% t-BuOK in toluene at 120 °C under N2 for 3 h]) were determined, where a complete conversion and near quantitative yield were achieved (entry 1). The role of bases has been examined: no conversion occurred in the absence of the base (entry 2); KOH (entry 3) can give a high yield of 85%, and thus will be an optional catalyst when a large-scale preparation is considered; and other bases, such as t-BuONa (entry 4), NaOH (entry 5), CsOH-H2O (entry 6) and K2CO3 (entry 7), seemed to be inferior or ineffective. The reaction temperature also was crucial for this reaction since a modest drop of reaction temperatures from 120 °C to 100 °C led to an incomplete conversion, an extremely low yield, and a substantial quantity of 9-benzylidenefluorene byproduct 4 (entry 8).7 Toluene (entry 1) and dioxane (entry 9) were the choice of solvents, but THF (entry 10) was not suitable for the reaction. Subsequently, a systematic investigation was made on the amount of t-BuOK used, suggesting that with increasing the base from 50 mol% (entry 1) to 100 mol%...
(entry 11), 150 mol% (entry 12) and 200 mol% (entry 13), the desired product decreased and the byproduct 9-fluorenone increased gradually; when it was reduced from 50 mol% (entry 1) to 25 mol% (entry 14), and 10 mol% (entry 15), the reaction could proceed to completion with no side reaction as long as the reaction lasted long enough.

Next, fluorene reacted with a range of representative alcohols to determine the generality of this protocol (Table 2). Generally, benzylic alcohols, whether the nonactivated (3a, 3f, 3k, and 3l), activated (3g, 3h, 3i, and 3j) or deactivated (3b, 3c, and 3d), smoothly underwent the reaction to afford the desired products with almost quantitative conversions and yields. Ortho-substituted benzylic alcohol (3e) needed a prolonged reaction time due to its steric effect, giving an excellent yield of 95%. Additionally, the mild reaction conditions tolerated some functional groups like the fluoro (3g), chloro (3h), bromo (3i and 3s), iodo (3j) or trifluoromethyl (3l) group. As we know, such halogen-containing derivatives would be very useful in organic synthesis as they might be further transformed and compounds containing trifluoromethyl functional groups are important pharmaceutical intermediates. Likewise, the reaction of fused aryl (3k and 3l), heteroaryl (3m) carbinols and piperonyl alcohol (3n) proceeded smoothly in near quantitative conversions under the moderately modified reaction conditions. Although aliphatic alcohols are much less reactive as alkylating reagents than benzylic alcohols, that isn’t the case in our reaction. Primary aliphatic alcohols (3n, 3o and 3p) were quantitatively converted to the desired 9-monoalkyfluorenes; even sterically congested secondary alcohols such as isopropanol (3q), 1-phenyl ethanol (3r) and cyclohexanol (3s) furnished the corresponding products in high yields at a more elevated temperature of 140 °C.

To ascertain the mechanism of the reaction, several additional control experiments were designed and carried out (Scheme 1). In a blank experiment, the freshly distilled p-methoxybenzyl alcohol was treated with potassium tert-butoxide (0.5 equivalents) at 120 °C in N₂, 3 h. The crude product examined quantitatively by 1H NMR and qualitatively by TLC; NMR yields determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Reaction time: 24 h. Reaction time: 48 h.

### Table 1

| Entry | Variation from the standard conditions | 3c<sup>a</sup> | 1<sup>b</sup> | 4<sup>b</sup> | Fluorenone<sup>b</sup> |
|-------|--------------------------------------|--------|--------|--------|------------------|
| 1     | None                                 | 99     | 0      | 0      | 0                |
| 2     | With no use of base                   | 0      | 100    | 0      | 0                |
| 3     | KOH instead of t-BuOK                 | 85     | 10     | 0      | 0                |
| 4     | t-BuONa instead of t-BuOK             | ~5     | 71     | 21     | 0                |
| 5     | NaOH instead of t-BuOK                | Trace  | 72     | 25     | 0                |
| 6     | CsOH·H₂O instead of t-BuOK            | 26     | 54     | ~5     | 0                |
| 7     | K₂CO₃ instead of t-BuOK               | 0      | 100    | 0      | 0                |
| 8     | 100 °C instead of 120 °C              | 10     | 48     | 40     | 0                |
| 9     | 1,4-Dioxane instead of toluene        | 92     | ~5     | 0      | 0                |
| 10    | THF instead of toluene                | Trace  | 88     | 10     | 0                |
| 11    | 0.5 mmol (100 mol%) t-BuOK            | 90     | ~5     | ~5     | Trace            |
| 12    | 0.75 mmol (150 mol%) t-BuOK           | 60     | ~5     | ~5     | 28               |
| 13    | 1.0 mmol (200 mol%) t-BuOK            | 50     | ~5     | 0      | 40               |
| 14<sup>c</sup> | 0.125 mmol (25 mol%) t-BuOK               | 99     | 0      | 0      | 0                |
| 15<sup>d</sup> | 0.05 mmol (10 mol%) t-BuOK             | 99     | 0      | 0      | 0                |

<sup>a</sup> The standard conditions: fluorene (0.5 mmol), 4-methoxybenzyl alcohol (1.5 mmol), base (0.25 mmol, 50 mol% relative to fluorene), solvent (4 mL), 120 °C, in N₂, 3 h. <sup>b</sup> The crude product examined quantitatively by 1H NMR and qualitatively by TLC; NMR yields determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> Reaction time: 24 h. <sup>d</sup> Reaction time: 48 h.
### Table 2 Synthesis of 9-monoalkylfluorene derivatives<sup>a</sup>

| Entry | Alcohol | Product | Isolated yield (%) |
|-------|---------|---------|--------------------|
| 1     | ![Alcohol 2a](image1.png) | ![Product 3a](image2.png) | 98                 |
| 2     | ![Alcohol 2b](image3.png) | ![Product 3b](image4.png) | 99                 |
| 3     | ![Alcohol 2c](image5.png) | ![Product 3c](image6.png) | 96                 |
| 4     | ![Alcohol 2d](image7.png) | ![Product 3d](image8.png) | 99                 |
| 5<sup>b</sup> | ![Alcohol 2e](image9.png) | ![Product 3e](image10.png) | 95                 |
| 6     | ![Alcohol 2f](image11.png) | ![Product 3f](image12.png) | 99                 |
| 7     | ![Alcohol 2g](image13.png) | ![Product 3g](image14.png) | 99                 |
| 8     | ![Alcohol 2h](image15.png) | ![Product 3h](image16.png) | 99                 |
| 9     | ![Alcohol 2i](image17.png) | ![Product 3i](image18.png) | 99                 |
| 10    | ![Alcohol 2j](image19.png) | ![Product 3j](image20.png) | 99                 |
| 11<sup>b,c</sup> | ![Alcohol 2k](image21.png) | ![Product 3k](image22.png) | 99                 |

**Table 2 (Contd.)**

| Entry | Alcohol | Product | Isolated yield (%) |
|-------|---------|---------|--------------------|
| 12<sup>b,c</sup> | ![Alcohol 2l](image23.png) | ![Product 3l](image24.png) | 99                 |
| 13<sup>b,d</sup> | ![Alcohol 2m](image25.png) | ![Product 3m](image26.png) | 97                 |
| 14<sup>b,c</sup> | ![Alcohol 2n](image27.png) | ![Product 3n](image28.png) | 99                 |
| 15<sup>b,c</sup> | ![Alcohol 2o](image29.png) | ![Product 3o](image30.png) | 99                 |
| 16<sup>b,d</sup> | ![Alcohol 2p](image31.png) | ![Product 3p](image32.png) | 99                 |
| 17<sup>b,c,e</sup> | ![Alcohol 2q](image33.png) | ![Product 3q](image34.png) | 89                 |
| 18<sup>b,c,f</sup> | ![Alcohol 2r](image35.png) | ![Product 3r](image36.png) | 90                 |
| 19<sup>f</sup> | ![Alcohol 2c](image37.png) | ![Product 3s](image38.png) | 99                 |
| 20<sup>b,d,f</sup> | ![Alcohol 2t](image39.png) | ![Product 3t](image40.png) | 85                 |
| 21<sup>f</sup> | ![Alcohol 2u](image41.png) | ![Product 3u](image42.png) | 99                 |
| 22<sup>b,e,f</sup> | ![Alcohol 2v](image43.png) | ![Product 3v](image44.png) | 81                 |

<sup>a</sup> Reaction conditions: fluorene (0.5 mmol), alcohols (1.5 mmol), t-BuOK (0.25 mmol), toluene (4 mL), in N<sub>2</sub>. <sup>b</sup> 24 h. <sup>c</sup> t-BuOK (0.375 mmol). <sup>d</sup> t-BuOK (0.50 mmol). <sup>e</sup> t-BuOK (0.75 mmol). <sup>f</sup> 140 °C. <sup>g</sup> 2-Bromo-9-fluorene was used.
Conclusions

In summary, we have developed a simple, mild and efficient protocol for the alkylation of fluorene with alcohols in the presence of potassium tert-butoxide as catalyst. This method affords a highly green access to 9-monoalkylfluorenes. Further study to expand the scope of substrates is ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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