



Cite this: *RSC Adv.*, 2019, 9, 35913

Received 18th September 2019

Accepted 29th October 2019

DOI: 10.1039/c9ra07557g

rsc.li/rsc-advances

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

Jiang-Tao Fan,^{ab} Xin-Heng Fan,^{ab} Cai-Yan Gao,^a Zhenpeng Wang^c and Lian-Ming Yang^{id}*^a

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.

Introduction

Fluorene motifs are a very useful class of building blocks for the construction of organic materials potentially applicable in optoelectronics, semiconductors, and solar cells.¹ Given their importance, chemical modifications or transformations of the parent fluorene have been an intriguing and valuable subject of research in organic synthesis. Among them is fluorene alkylation. Typically, 9-monoalkylated fluorenes were prepared from the condensation of fluorene and aldehydes and their subsequent hydrogenation² or *via* a classical S_N2 reaction of 9-lithiofluorene with haloalkanes.³ These traditional methods commonly suffer from harsh reaction conditions, a complex product distribution, and difficult experimental operations. A simple alternative to 9-monoalkylfluorenes is the alkylation of fluorene with alcohols using bases as the promoting agents.⁴ However, this approach required both extremely high temperatures (150–210 °C) and highly concentrated strong bases (more than stoichiometric quantities), resulting in the occurrence of many side reactions. A very recent publication disclosed a greener method for the aldehyde/ketone-catalysed alkylation of fluorene,⁵ where significant improvements were made on reaction conditions, selectivity, efficiency, and substrate scope. But an evident limitation of the method lies in the fact that individual substrates require a corresponding, specific aldehyde/ketone catalyst. Accordingly, to further improve this synthetic reaction remains a requirement.

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-benzylidene fluorene 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%

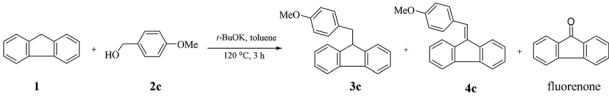
^aBeijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Green Printing, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China. E-mail: yanglm@iccas.ac.cn; xinxin9968@iccas.ac.cn; Fax: +8610-62559373

^bUniversity of Chinese Academy of Sciences, Beijing 100049, China

^cNational Centre for Mass Spectrometry in Beijing, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra07557g



Table 1 Screening of reaction conditions^a


Entry	Variation from the standard conditions	3c ^b	1 ^b	4 ^b	Fluorenone ^b
1	None	99	0	0	0
2	With no use of base	0	100	0	0
3	KOH instead of <i>t</i> -BuOK	85	10	0	0
4	<i>t</i> -BuONa instead of <i>t</i> -BuOK	~5	71	21	0
5	NaOH instead of <i>t</i> -BuOK	Trace	72	25	0
6	CsOH·H ₂ O instead of <i>t</i> -BuOK	26	54	~5	0
7	K ₂ CO ₃ instead of <i>t</i> -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%) <i>t</i> -BuOK	90	~5	~5	Trace
12	0.75 mmol (150 mol%) <i>t</i> -BuOK	60	~5	~5	28
13	1.0 mmol (200 mol%) <i>t</i> -BuOK	50	~5	0	40
14 ^c	0.125 mmol (25 mol%) <i>t</i> -BuOK	99	0	0	0
15 ^d	0.05 mmol (10 mol%) <i>t</i> -BuOK	99	0	0	0

^a 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. ^b 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. ^c Reaction time: 24 h. ^d Reaction time: 48 h.

(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.

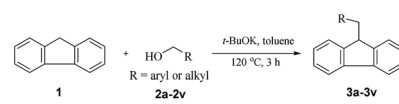
Next, fluorene reacted with a range of representative alcohols to determine the generality of this protocol (Table 2). Generally, benzylic alcohols, whether the nonactivated (**3a**, **3f**, **3k**, and **3l**), activated (**3g**, **3h**, **3i**, and **3j**) or deactivated (**3b**, **3c**, and **3d**), 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 (**3t**) 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 (**3u**) 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,⁵ that isn't the case in our reaction. Primary aliphatic alcohols (**3n**, **3o** and **3p**) were quantitatively converted to the desired 9-monoalkylfluorenes; even sterically congested secondary

alcohols such as isopropanol (**3q**), 1-phenyl ethanol (**3r**) and cyclohexanol (**3v**) 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 for 3 h, affording an around 5% yield of anisaldehyde **5c** (Scheme 1-i). 9-Benzylidene-fluorene **4c** was readily obtained in 72% isolated yield from the reaction of fluorene and benzaldehyde under the standard conditions (Scheme 1-ii). In the process of transfer hydrogenation of **4c** with **2c**, the target product **3c** and equimolar aldehyde **5c** (**5c**/**3c** = 0.98/1.00 mol mol⁻¹ by ¹H NMR analysis of the reaction mixture) would be generated simultaneously (Scheme 1-iii).

Combining our own experimentation with the relevant publications,^{4,5} we proposed a plausible mechanistic path for this reaction (Scheme 2). As shown in Scheme 2, a small amount of aldehyde **5** corresponding to alcohol **2** would first occur under the reaction conditions given. It was well established that an aldehyde **5** condenses with fluorene **1** to give a dibenzofulvene **4** in the presence of the base.⁸ Next, potassium alkoxide reduces the exo-double bond with attendant formation of a molecule of aldehyde. This step may formally be regarded as a type of Meerwein-Ponndorf-Verley reduction⁹ where the exo-double bond of the dipolar fulvene plays the role of the hydrogen acceptor. Finally, the potassium derivative of the product **6** reacts with the alcohol to give 9-alkylfluorene **3**.



Table 2 Synthesis of 9-monoalkylfluorene derivatives^a


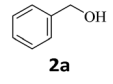
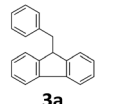
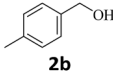
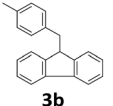
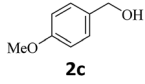
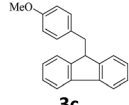
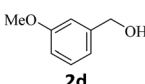
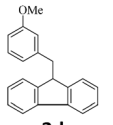
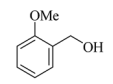
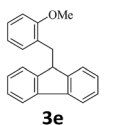
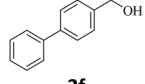
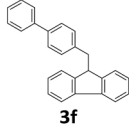
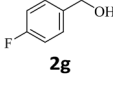
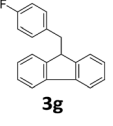
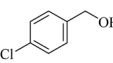
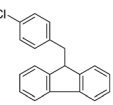
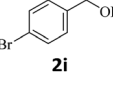
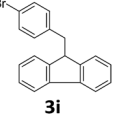
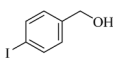
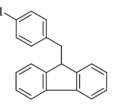
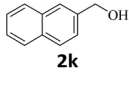
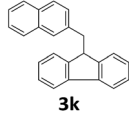
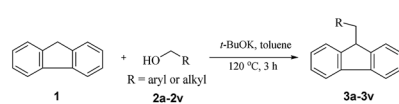
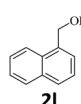
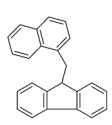

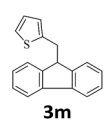
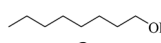
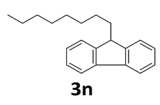

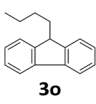
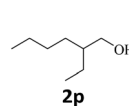
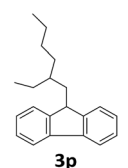

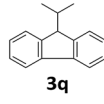
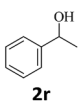
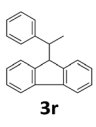
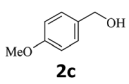
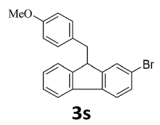
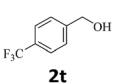
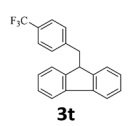

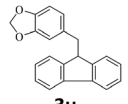

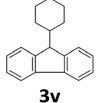
Entry	Alcohol	Product	Isolated yield (%)
1			98
2			99
3			96
4			99
5 ^b			95
6			99
7			99
8			99
9			99
10			99
11 ^{b,c}			99

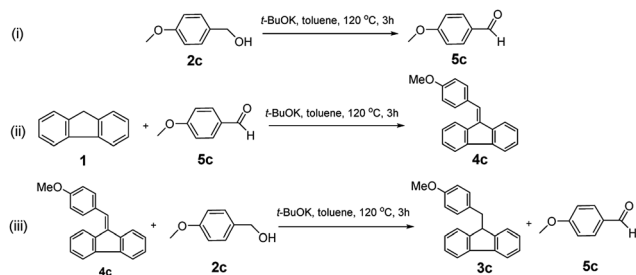
Table 2 (Contd.)



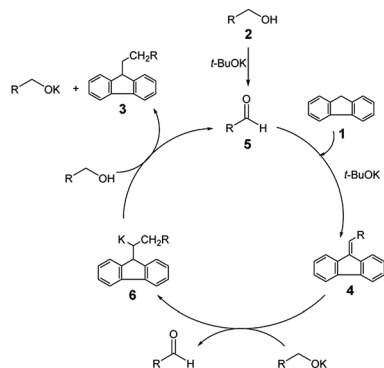
Entry	Alcohol	Product	Isolated yield (%)
12 ^{b,c}			99
13 ^{b,d}			97
14 ^{b,c}			99
15 ^{b,c}			99
16 ^{b,d}			99
17 ^{b,e,f}			89
18 ^{b,e,f}			90
19 ^g			99
20 ^{b,e,f}			85
21 ^c			99
22 ^{b,e,f}			81

^a Reaction conditions: fluorene (0.5 mmol), alcohols (1.5 mmol), *t*-BuOK (0.25 mmol), toluene (4 mL), in N₂. ^b 24 h. ^c *t*-BuOK (0.375 mmol). ^d *t*-BuOK (0.50 mmol). ^e *t*-BuOK (0.75 mmol). ^f 140 °C. ^g 2-Bromo-9-fluorene was used.





Scheme 1 Control experiments.



Scheme 2 A proposed catalytic cycle.

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.

Acknowledgements

The authors thank National Natural Science Foundation of China (Project No. 21503234 and 21572235) for financial support of this work.

Notes and references

- (a) N. R. Evans, L. S. Devi, C. S. K. Mak, S. E. Watkins, S. I. Pascu, A. Köhler, R. H. Friend, C. K. Williams and A. B. Holmes, *J. Am. Chem. Soc.*, 2006, **128**, 6647; (b) G. Hughes and M. R. Bryce, *J. Mater. Chem.*, 2005, **15**, 94; (c) U. Scherf and E. J. W. List, *Adv. Mater.*, 2002, **14**, 477; (d) M. T. Bernius, M. Inbasekaran, J. O'Brien and W. Wu, *Adv. Mater.*, 2000, **12**, 1737; (e) K. Miyatake, B. Bae and M. Watanabe, *Polym. Chem.*, 2011, **2**, 1919; (f) O. Inganäs, F. Zhang and M. R. Andersson, *Acc. Chem. Res.*, 2009, **42**, 1731; (g) G. Dennler, M. C. Scharber and C. J. Brabec, *Adv. Mater.*, 2009, **21**, 1323.
- The formation and hydrogenation of 9-alkylidene fluorenes: (a) G. B. Bachman and S. Polansky, *J. Org. Chem.*, 1951, **16**, 1690; (b) C. A. Fleckenstein, R. Kadyrov and H. Plenio, *Org. Process Res. Dev.*, 2008, **12**, 475.
- The S_N2 reaction of 9-lithiofluorene with haloalkanes: (a) G. S. Hamilton, R. E. Mewshaw, C. M. Bryant, Y. Feng, G. Endemann, K. S. Madden, J. E. Janczak, J. Perumattam, L. W. Stanton, X. Yang, Z. Yin, B. Venkataramen and D. Y. Liu, *J. Med. Chem.*, 1995, **38**, 1650; (b) Q. Pei and Y. Yang, *J. Am. Chem. Soc.*, 1996, **118**, 7416; (c) C. A. Fleckenstein and H. Plenio, *Chem. – Eur. J.*, 2007, **13**, 2701; (d) F. Turhan, F. Pak, A. Yesildag, Z. Kudas and D. Ekinici, *Polym. Bull.*, 2012, **68**, 1677.
- The base-catalyzed 9-monoalkylation of fluorene with alcohols: (a) K. L. Schoen and E. I. Becker, *J. Am. Chem. Soc.*, 1955, **77**, 6030; (b) K. L. Schoen and E. I. Becker, *Organic Synthesis*, Wiley, New York, 1963, Collect. vol. IV, p. 623; (c) Also see: ref. 2b.
- The aldehyde/ketone-catalyzed 9-monoalkylation of fluorene with alcohols: J. Chen, Y. Li, S. Li, J. Liu, F. Zheng, Z. Zhang and Q. Xu, *Green Chem.*, 2017, **19**, 623.
- For selected reviews on the use of alcohols as alkylating reagents, see: (a) A. J. A. Watson and J. M. J. Williams, *Science*, 2010, **329**, 635; (b) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753; (c) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853; (d) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (e) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (f) A. Corma, J. Navas and M. J. Sabater, *Chem. Rev.*, 2018, **118**, 1410; (g) G. Chelucci, *Coord. Chem. Rev.*, 2017, **331**, 1; (h) C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 1229712.
- It was found that the 9-alkylidene fluorene 4 would become a major product under the same conditions as for the 9-monoalkyl fluorene synthesis except at a lower reaction temperature of about 70 °C. Also see: Table S1 in ESI.†
- R. F. Schultz and C. F. Smullin, *J. Am. Chem. Soc.*, 1940, **62**, 2904.
- For selected Meerwein–Ponndorf–Verley reduction reactions, see: (a) J. Lee, T. Ryu, S. Park and P. H. Lee, *J. Org. Chem.*, 2012, **77**, 4821; (b) C. Battilocchio, J. M. Hawkins and S. V. Ley, *Org. Lett.*, 2013, **15**, 2278; (c) J. Song, B. Zhou, H. Zhou, L. Wu, Q. Meng, Z. Liu and B. Han, *Angew. Chem., Int. Ed.*, 2015, **54**, 9399.

