



Synthetic Communications An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Nickel-catalyzed synthesis of 9-monoalkylated fluorenes from 9-fluorenone hydrazone and alcohols

Jiang-Tao Fan, Xin-Heng Fan, Yong-Jie Chen, Cai-Yan Gao & Lian-Ming Yang

To cite this article: Jiang-Tao Fan, Xin-Heng Fan, Yong-Jie Chen, Cai-Yan Gao & Lian-Ming Yang (2019): Nickel-catalyzed synthesis of 9-monoalkylated fluorenes from 9-fluorenone hydrazone and alcohols, Synthetic Communications, DOI: <u>10.1080/00397911.2019.1647438</u>

To link to this article: <u>https://doi.org/10.1080/00397911.2019.1647438</u>



View supplementary material 🖸



Published online: 01 Aug 2019.

|--|

Submit your article to this journal \square

Article views: 18



🔾 View related articles 🗹

🕨 View Crossmark data 🗹



Check for updates

Nickel-catalyzed synthesis of 9-monoalkylated fluorenes from 9-fluorenone hydrazone and alcohols

Jiang-Tao Fan^{a,b}, Xin-Heng Fan^a, Yong-Jie Chen^{a,b}, Cai-Yan Gao^a, and Lian-Ming Yang^a

^aBeijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Green Printing, Institute of Chemistry, Chinese Academy of Sciences, Beijing, P. R. China; ^bUniversity of Chinese Academy of Sciences, Beijing, P. R. China

ABSTRACT

A practical protocol was disclosed for the nickel-catalyzed C-alkylation of 9-fluorenone hydrazone with alcohols using *t*-BuOK as the base, and 9-monoalkylated fluorene derivatives were obtained in good yields under the benign conditions.

GRAPHICAL ABSTRACT



ARTICLE HISTORY Received 19 April 2019

KEYWORDS

Benzylic alcohol; 9monoalkylated fluorene; nickel catalyst;

Introduction

Fluorene motifs are a very useful class of building blocks for organic materials applicable in optoelectronics, semiconductors, and solar cells.^[1] Accordingly, the construction of fluorene derivatives, particularly 9-substituted fluorenes, became a valuable subject in synthetic chemistry, and some useful methods have been developed. Representative examples include: (i) the classical S_N2 reaction of 9-lithofluorene with haloalkanes^{;[2]} (ii) the formation of alkylidenefluorenes via condensation of fluorene and aldehydes and their subsequent hydrogenation;^[3] (iii) the palladium-catalyzed cross-coupling reaction of fluorene with aryl halide;^[4] (iv) the direct 9-monoalkylation of fluorene with benzylic alcohols under the forced conditions;^[5] and (v) the aldehyde/ketone-catalyzed alkylation of fluorene with benzylic alcohols.^[6] Apparently, all the reactions mentioned above are based on the fluorene as a nucleophile. In recent years, there has appeared a series of reports on the novel reactions involving aldehyde/ketone hydrazones as the latent carbanion equivalents.^[7-9] On the other hand, it has proven that alcohols, which are greener and safer than halohydrocarbon-type compounds, can be used as alkylating reagents in the presence of transition-metal catalysts.^[10] Inspired by those studies, we combined 9-fluorenone

Supplemental data for this article is available online at on the publisher's website © 2019 Taylor & Francis Group, LLC

CONTACT Lian-Ming Yang 😒 yanglm@iccas.ac.cn; Xin-Heng Fan 😒 xinxin9968@iccas.ac.cn 🗈 Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Green Printing, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, P. R. China

	H ₂ N		Me		
		но	Ni/Ligand, Base Solvent, 110 °C, 9 h		
Entry	[Ni(II)] (mol%)	Ligand(mol%)	Base	Solvent	Yield ^b (%)
1	None	None	t-BuOK	Dioxane	29
2	$NiBr_2$ (5)	DPPP ^c (5)	t-BuOK	Dioxane	48
3	$Ni(acac)_2$ (5)	DPPP (5)	t-BuOK	Dioxane	67
4	$NiCl_2(PPh_3)_2$ (5)	DPPP (5)	t-BuOK	Dioxane	67
5	Cat1 ^d (5)	DPPP (5)	t-BuOK	Dioxane	80
6	Cat1 (5)	PPh ₃ (10)	t-BuOK	Dioxane	60
7	Cat1 (5)	DPPE ^e (5)	t-BuOK	Dioxane	69
8	Cat1 (5)	DPPF ^f (5)	t-BuOK	Dioxane	69
9	Cat1 (5)	Phena ^g (5)	t-BuOK	Dioxane	68
10	Cat1 (5)	DPPP (5)	t-BuONa	Dioxane	16
11	Cat1 (5)	DPPP (5)	КОН	Dioxane	21
12	Cat1 (5)	DPPP (5)	K ₃ PO ₄	Dioxane	Trace
13	Cat1 (5)	DPPP (5)	K ₂ CO ₃	Dioxane	Trace
14	Cat1 (5)	DPPP (5)	t-BuOK	THF	34
15	Cat1 (5)	DPPP (5)	t-BuOK	Toluene	54
16	Cat1 (3)	DPPP (3)	t-BuOK	Dioxane	73
17 ^h	Cat1 (5)	DPPP (5)	t-BuOK	Dioxane	25

Table 1. Screening of conditions for the Ni-catalyzed reaction of 9-fluorenone hydrazone and 4-methoxybenzyl alcohol^a.

^aReaction conditions: 9-fluorenone hydrazone (0.5 mmol), 4-methoxybenzyl alcohol (1.5 mmol), base (0.75 mmol), solvent (4 mL), in N₂, 110°C, 9 h.

^bNMR yields: determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

^cDPPP: 1,3-bis(diphenyphosphino)propane.

^dCat.-1: Ni(PPh₃)₂(1-naphthyl)Cl.

^eDPPE: 1,2-bis(diphenylphosphino)ethane.

^fDPPF: 1,1'-bis(diphenylphosphino)ferrocene.

^gPhena: 1,10-phenanthroline.

^h100°C.

hydrazone as the latent carbanion with alcohols as alkylating reagents to develop a new route to 9-monoalkylated fluorenes. Herein, we wish to report our outcome.

Results and discussion

Initially, 9-fluorenone hydrazone and 4-methoxybenzyl alcohol were chosen as model substrates for screening reaction conditions, and the results are summarized in Table 1. We first performed the reaction only in the presence of the base;^[5] as a result, the desired product was produced in a low yield (entry 1). The reaction with no catalyst and its mechanism were documented in a very earlier publication.^[5a] The role of nickel catalysts was demonstrated in the further investigation (entries 2–5), among which Ni(PPh₃)₂(1-naphthyl)Cl (**Cat.-1**) was found to be the most effective (entry 5) with the yield of 80%. As for this reaction investigated, the major byproduct was 9-fluorenone that should be from the decomposition of the starting 9-fluorenone hydrazone. Several commonly used ligands were surveyed, suggesting that PPh₃, DPPE, DPPF, and 1,10-phenanthroline were all inferior to DPPP (entry 5 *vs.* entries 6–9). The nature of the base was extremely important for this reaction since *t*-BuOK was far superior to *t*-BuONa, KOH, K₃PO₄ or K₂CO₃ (entry 5 vs. entries 10–13). Different from those reactions reported recently,^[7,9] the addition of CsF did not improve the reaction yield at all. For the solvents used, dioxane appeared to be the solvent of choice compared with

H ₂ N _N	+ HO R R = aryl or all	C1/DPPP, <i>t</i> -BuOK dioxane, 110 °C, 9 h cyl	R
1	2a-2s		3a-3u
Entry	Alcohol	Product	Isolated yield (%)
1	С Он 2а	39	73
2	он 2b		64
3	Meo OH		62
4	MeO OH 2d	3c	62
5	ОМе	OMe Contraction	47
6	Ze OH 2f	3e	66
7	_F 2g	sg	71
8	ст Он 2h	ch c	71

Table 2. Ni-catalyzed synthesis of 9-monoalkylated fluorenes by the reaction of 9-fluorenone hydrazone and alcohols^a.

(continued)

4 🍝 J.-T. FAN ET AL.

9	ви ОН 2i	3i	55
10	тон 2j	4j	40 25
11	Сторон 2k	3k	52
12	2 I	Since 3 m	64
13	<u>с</u> у он 2m	3n	78
14 ^b	_ _{ОН} 2n		55
15 ^b	он 20	3p	60
15 ^b 16 ^b	20 20 	3p	60 51

(continued)



^aReaction conditions: 9-fluorenone hydrazone (0.5 mmol), benzylic alcohols (1.5 mmol), **Cat.-1** (5 mol%), DPPP (5 mol%), t-BuOK (0.75 mmol), 1,4-dioxane (4 mL), in N₂.

^b24 h.

^c2-bromo-9-fluorenone hydrazine (0.5 mmol).

other solvents such as THF (entry 14) and toluene (entry 15). Reducing the loading of the catalyst adversely affected the reaction (entry 16), and lowering the reaction temperature caused a drastic drop in yields (entry 17). Finally, our standard conditions were set up as entry 5 in Table 1.

With optimized reaction conditions in hand, we then investigated the scope and limitations of the reaction, and the results were summarized in Table 2. As shown in Table 2, benzylic alcohols, whether electron-neutral (entries 1, 3a and 6, 3f), -rich (entries 2-4, 3b-3d), or -poor (entries 7-9, 3g-3i), delivered the corresponding 9monoalkylated fluorenes in good yields; but o-methoxybenzyl alcohol gave only a lower yield (entry 5, 3e), indicating that the reaction was sensitive to the steric effect. It should be noted that halogen atoms in the substrates were well tolerated in the reaction system (entries 7-9, 3g-3i). Such halogen-containing products as in the cases of entries 8 and 9 (3h and 3i) would be very useful in organic synthesis since they can be further transformed. Exceptionally, the reaction of p-iodobenzyl alcohol (entry 10, 4j and 3k) gave a 25% yield of 9-benzylfluorene and 40% yield of 9-benzylidenefluorene, rather than the expected molecule 9-(4-iodobenzyl)fluorene. The reason might be that primary deiodination of p-iodobenzyl alcohol proceeds with a single electron transfer (SET) mechanism, leading to the deiodination of iodobenzyl alcohol.^[5c,11] This result may be of interest from the synthetic and mechanistic points of view. It seems to be that fused aromatic (entries 11, 3l and 12, 3m) and heteroaryl (entry 13, 3n) carbinols were also suitable substrates for this reaction. To our pleasure, primary aliphatic alcohols and the sterically demanding secondary alcohol afforded the desired products with good yields over a prolonged reaction time (entries 14-17, 30-3r). Secondary benzylic alcohol, 1phenyl ethanol, gave only 31% isolated yield with a ratio of 95% of the desired product to 5% of 9-(1-phenylethylidene)-9H-fluorene (determined by ¹H NMR) (entry 18, 3s and 4t). In part of nucleophilic partners, 2-bromo-9-fluorenone hydrazone was utilized, giving the corresponding product in 55% yield (entry 19, 3u). The reaction of 1,2-



Scheme 1. A proposed catalytic cycle.

propanediol only gave fluorene and 9,9'-bifluorenyl as the products. Additionally, two control experiments were carried out by the use of aldehyde and tertiary alcohol as the starting reactants, which produce no desired products, but 1-(9*H*-fluoren-9-ylidene)-2-(4-methoxybenzylidene)hydrazone and 9,9'-bifluorenylidene, respectively.

By combining the relevant literature ^[8b,12] with our experimental results, we proposed a plausible mechanistic path for this reaction (Scheme 1). As shown in Scheme 1, a Ni(0) complex **B** is formed via the coordination of the Ni(II) precursor with alcohol and the subsequent β -hydride elimination. Insertion of the complex **B** into the C–O bond of an alcohol (an oxidative addition process) provides the intermediate **C**, which further undergoes an alcohol exchange to produce the corresponding water and nickel complex **D**. Then, the complex **D** underwent transmetalation with carbon-nucleophile **E** derived from deprotonation of hydrazone 1 to form intermediate **F**. Reductive elimination gave the diimide **G** and regenerated Ni (0) catalyst. Finally, the desired product **3** was formed by the wolf-kishner reaction, and the byproduct **4** might be obtained by a base-assisted β -elimination of **G**.

Conclusions

In summary, we have developed a practical new approach to the synthesis of 9-monoalkylfluorenes from 9-fluorenone hydrazones and alcohols, which would constitute a valuable part of fluorene chemistry. Further work to expand the scope of substrates and elucidate the mechanistic details is currently underway in our lab.

Experimental

General procedure for Ni-catalyzed reaction of 9-fluorenone hydrazone and benzylic alcohols: An oven-dried 25-mL flask was charged with *t*-BuOK (0.75 mmol), Ni(PPh₃)₂(1-naphthyl)Cl (0.025 mmol) and DPPP (0.025 mmol). Then the 9-fluorenone hydrazone (0.5 mmol) and the benzyl alcohol (1.5 mmol) (if solid) were added. The flask was evacuated and backfilled with nitrogen, with the operation being repeated twice. Dried 1,4-dioxane (4 mL) and the benzyl alcohol (1.5 mmol) (if liquid) were added via syringe at this time. The reaction mixture was performed on WATTECS WP-TEC-1020 parallel reactor of 110 °C for 9 h and then allowed to cool to room temperature; it was then filtered through a silica-gel pad that was washed with ethyl acetate. The combined organic phases were evaporated under reduced pressure and the residue purified by silica-gel column chromatography to give the desired products.

Full experimental details, and ¹H and ¹³C NMR spectra can be seen in Supplementary Material.

Funding

The authors thank National Natural Science Foundation of China (Project Nos. 21503234 and 21572235) for financial support of this work.

References

- [1] (a) Evans, N. R.; Devi, L. S.; Mak, C. S. K.; Watkins, S. E.; Pascu, S. I.; Köhler, A.; Friend, R. H.; Williams, C. K.; Holmes, A. B. J. Am. Chem. Soc. 2006, 128, 6647; DOI: 10.1021/ ja0584267. (b) Hughes, G.; Bryce, G. J. Mater. Chem. 2005, 15, 94; DOI: 10.1039/ b413249c. (c) Scherf, U.; List, E. J. W. Adv. Mater. 2002, 14, 477; DOI: 10.1002/1521- 4095(20020404)14:7<477::AID-ADMA477>3.0.CO;2-9. (d) Bernius, M. T.; Inbasekaran, M.; Brien, J. O, Wu, W. Adv. Mater. 2000, 12, 1737; DOI: 10.1002/1521- 4095(200012)12:23<1737::AID-ADMA1737>3.0.CO;2-N. (e) Miyatake, K.; Bae, B.; Watanabe, M. Polym. Chem. 2011, 2, 1919; DOI: 10.1039/c1py00103e. (f) Inganäs, O.; Zhang, F.; Andersson, M. R. Acc. Chem. Res. 2009, 42, 1731; DOI: 10.1021/ar900073s. (g) Dennler, G.; Scharber, G.; Brabec, C. J. Adv. Mater. 2009, 21, 1323. DOI: 10.1002/ adma.200801283.
- [2] The SN2 reaction of 9-lithofluorene with haloalkanes: (a) Hamilton, G. S.; Mewshaw, G. S.; Bryant, C. M.; Feng, Y.; Endemann, Y.; Madden, K. S.; Janczak, K. S.; Perumattam, J.; Stanton, L. W.; Yang, X.; et al. J. Med. Chem. 1995, 38, 1650; DOI: 10.1021/jm00010a009. (b) Fleckenstein, H.; Plenio, C. A. Chem. Eur. J. 2007, 13, 2701; DOI: 10. 1002/chem.200601142. (c) Turhan, F.; Pak, F.; Yesildag, F.; Kudas, F.; Ekinci, D. Polym. Bull. 2012, 68, 1677; DOI: 10.1007/s00289-011-0667-9. (d) Pei, Q.; Yang, Y. J. Am. Chem. Soc. 1996, 118, 7416. DOI: 10.1021/ja9615233.
- [3] The formation of alkylidenefluorenes and their subsequent hydrogenation: (a) Schultz,
 R. F.; Smullin, C. F. J. Am. Chem. Soc. 1940, 62, 2904; DOI: 10.1021/ja01868a006.
 (b) Bachman, G. B.; Polansky, S. J. Org. Chem. 1951, 16, 1690; DOI: 10.1021/jo50005a005.

(c) Wawzonek, S.; Duffek, E.; Sial, N. M. J. Org. Chem. 1956, 21, 276. DOI: 10.1021/ jo01109a004.

- [4] The Pd-catalyzed cross-coupling of fluorene with aryl halide: (a) Chen, J.-J.; Onogi, S.;
 Hsieh, Y.-C.; Hsiao, C.-C.; Higashibayashi, C.-C.; Sakurai, H.; Wu, Y.-T. Adv. Synth. Catal. 2012, 354, 1551; DOI: 10.1002/adsc.201100931. (b) Ji, Y.-Y.; Lu, L.-L.; Shi, Y.-C.;
 Shao, L.-X. Org. Biomol. Chem. 2014, 12, 8488. DOI: 10.1039/C4OB01594K.
- [5] The base-catalyzed 9-monoalkylation of fluorene with alcohols: (a) Schoen, K. L.; Becker, E. I. J. Am. Chem. Soc. 1955, 77, 6030; DOI: 10.1021/ja01627a068. (b) Schoen, K. L.; Becker, E. I. Organic Synthesis; Wiley: New York, 1963; Vol. IV; pp 623; (c) S.-C. Chan, J.-P. Jang, Y.-J. Cherng, Tetrahedron. 2009, 65, 1977. DOI: 10.1016/j.tet.2009.01.029.
- [6] The aldehyde/ketone-catalyzed 9-monoalkylation of fluorene and benzylic alcohols:
 (a) Chen, J.; Li, Y.; Li, S.; Liu, J.; Zheng, F.; Zhang, Z.; Xu, Q. Green Chem. 2017, 19, 623; DOI: 10.1039/C6GC02518H. (b) Fleckenstein, C. A.; Kadyrov, R.; Plenio, H. Org. Process Res. Dev. 2008, 12, 475. DOI: 10.1021/op7001479.
- [7] Transition metal-catalyzed nucleophilic addition reactions of an aldehyde/ketone hydrazone as the carbanion equivalent: (a) Wang, H.; Dai, X.-J.; Li, C.-J. Nat. Chem. 2017, 9, 374; DOI: 10.1038/nchem.2677. (b) Chen, N.; Dai, X.-J.; Wang, H.; Li, C.-J. Angew. Chem.; Int. Ed. 2017, 56, 6260; DOI: 10.1002/anie.201610578. (c) Dai, X.-J.; Wang, H.; Li, C.-J. Angew. Chem.; Int. Ed. 2017, 56, 6302. DOI: 10.1002/anie.201700059. (d) Li, C.-C.; Dai, X.-J.; Wang, H.; Zhu, D.; Gao, J.; Li, C.-J. Org. Lett. 2018, 20, 3801. DOI: 10.1021/acs. orglett.8b01391.
- [8] Nickel-catalyzed C-C cross-couplings of an aldehyde/ketone hydrazone with an aryl halide or tosylate: (a) Tang, J.; Lv, L.; Dai, X.-J.; Li, C.-C.; Li, L.; Li, C.-J. *Chem. Commun.* 2018, 54, 1750; DOI: 10.1039/C7CC09290C. (b) Lv, L.; Zhu, D.; Tang, J.; Qiu, Z.; Li, C.-C.; Gao, J.; Li, C.-J. ACS Catal. 2018, 8, 4622. DOI: 10.1021/acscatal.8b01224.
- [9] Transition metal-catalyzed McMurry-type coupling reactions utilizing an aldehyde/ketone hydrazone as the latent carbanion equivalent. Wei, W.; Dai, X.-J.; Wang, H.; Li, C.-C.; Yang, X.; Li, C.-J. *Chem. Sci* **2017**, *8*, 8193. DOI: 10.1039/C7SC04207H.
- [10] Selected reviews on the use of alcohols as alkylating reagents: (a) Watson, A. J. A.; Williams, J. M. J. Science. 2010, 329, 635; DOI: 10.1126/science.1191843. (b) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. Dalton Trans. 2009, 753; DOI: 10.1039/B813383B. (c) Bähn, S.; Imm, S.; Neubert, L.; Zhang, L.; Neumann, H.; Beller, M. ChemCatChem. 2011, 3, 1853; DOI: 10.1002/cctc.201100255. (d) Dobereiner, G. E.; Crabtree, R. H. Chem. Rev. 2010, 110, 681; DOI: 10.1021/cr900202j. (e) Guillena, G.; Ramón, G.; Yus, M. Chem. Rev. 2010, 110, 1611; DOI: 10.1021/cr9002159. (f) Corma, A.; Navas, J.; Sabater, M. J. Chem. Rev. 2018, 118, 1410; DOI: 10.1021/acs.chemrev.7b00340. (g) Chelucci, G. Coord. Chem. Rev. 2017, 331, 1; DOI: 10.1016/j.ccr.2016.10.002. (h) Gunanathan, C.; Milstein, D. Science. 2013, 341, 1229712. DOI: 10.1126/science.1229712.
- [11] Pastor, S. D. Helv. Chim. Acta. 1988, 71, 859. DOI: 10.1002/hlca.19880710421.
- [12] The literature related to the reaction mechanism proposed: (a) Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. Angew. Chem. Int. Ed. 2010, 49, 4566; DOI: 10. 1002/anie.200907359. (b) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. Acc. Chem. Res. 2010, 43, 1486. DOI: 10.1021/ar100082d.