Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4419–4422

Unusual synthesis of dihydropyrido[2,1-*a*]isoindolone derivatives by radical cyclization of enamides of Baylis–Hillman adducts

Saravanan Gowrisankar,[a] Seong Jin Kim,[a] Ji-Eun Lee[b] and Jae Nyoung Kim[a,*]

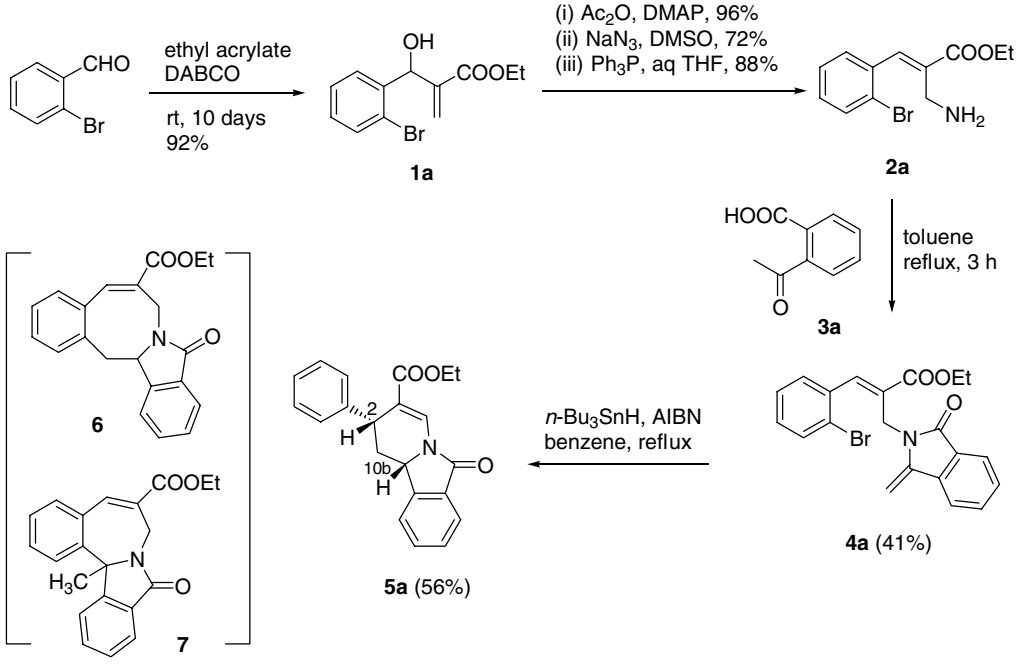
[a]*Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea*
[b]*Department of Chemistry (BK21) and Central Instrument Facility, Gyeongsang National University, Jinju 660-701, Republic of Korea*

Received 29 March 2007; accepted 16 April 2007
Available online 27 April 2007

Abstract—During the radical cyclization of enamide derivatives **4** we found unusual formation of dihydropyrido[2,1-*a*]isoindolone derivatives **5**. The enamides were synthesized in four steps from the Baylis–Hillman adducts of *ortho*-bromobenzaldehydes.

Recently a variety of chemical transformations using the Baylis–Hillman adducts have been investigated extensively.[1] Especially the usefulness of the Baylis–Hillman adducts for the synthesis of many heterocyclic compounds is noteworthy.[1] Radical cyclizations involving the Baylis–Hillman adducts have also been examined by us and other research groups.[2]

Radical cyclizations of enamide derivatives have been reported for the synthesis of many heterocyclic



Scheme 1.

Keywords: Dihydropyrido[2,1-*a*]isoindolone; Radical cyclization; Enamides; Baylis–Hillman adducts.
* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389; e-mail: kimjn@chonnam.ac.kr

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.111

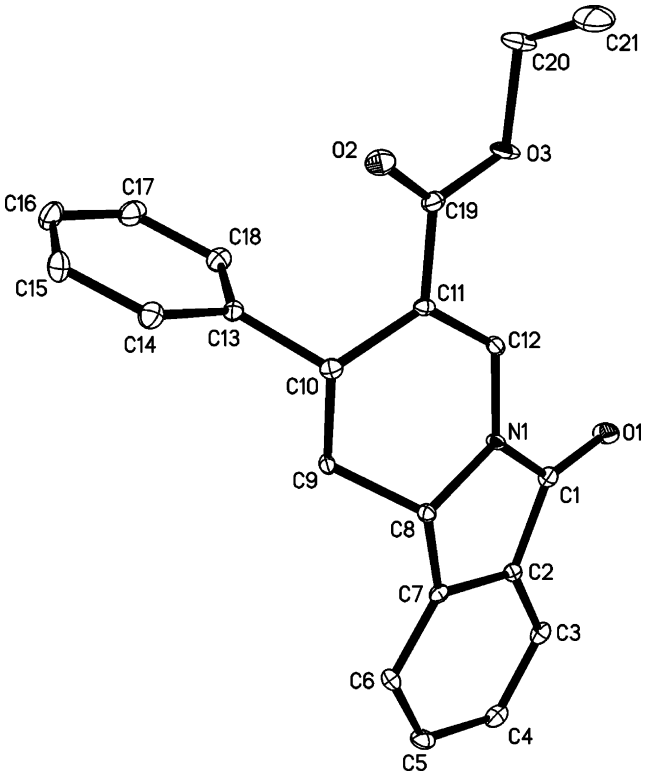
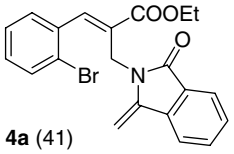
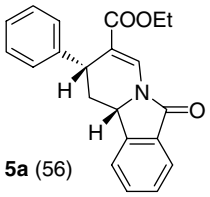
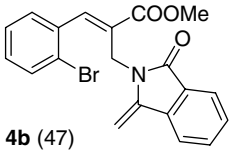
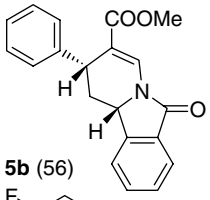
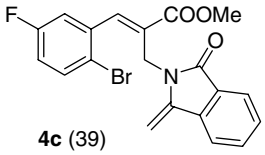
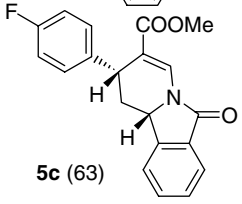
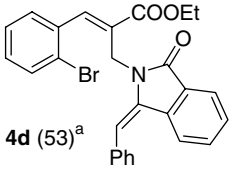
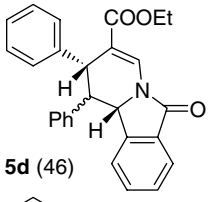
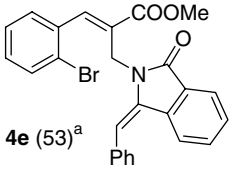
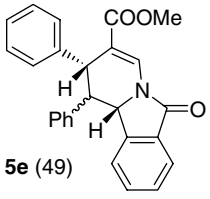


Figure 1. ORTEP drawing of compound **5a**.

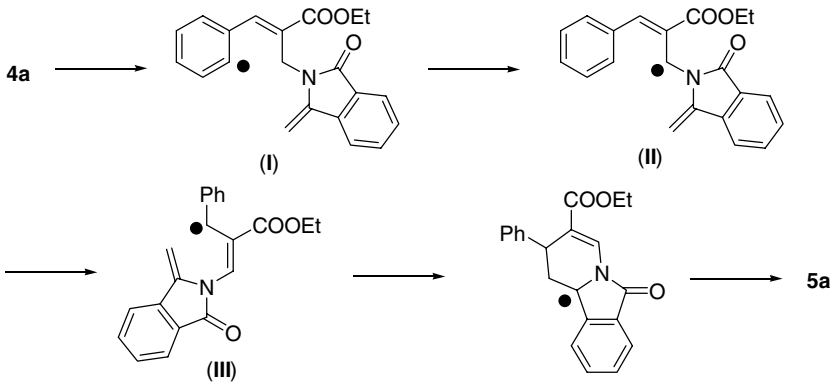
Table 1. Synthesis of dihydropyrido[2,1-*a*]isoindolone derivatives

Entry	Enamide **4** (% yield)	Product **5** (% yield)
1	 **4a** (41)	 **5a** (56)
2	 **4b** (47)	 **5b** (56)
3	 **4c** (39)	 **5c** (63)
4	 **4d** (53)[a]	 **5d** (46)
5	 **4e** (53)[a]	 **5e** (49)

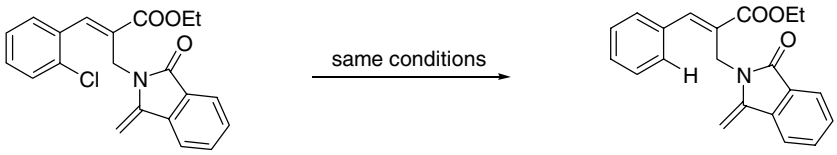
[a] We used benzalphthalide (**3b**) instead of **3a**.

compounds[3] including isoindolobenzazepines,[3a,b] tetrahydroisoquinolines,[3c] erythrina alkaloids,[3d] and mappicine ketone Nothapodytine B.[3e] During the studies on the chemical transformations of Baylis–Hillman adducts[2] we were interested in the synthesis of eight-membered cyclic compounds (vide infra) via the radical cyclization reaction of enamide derivatives derived from Baylis–Hillman adducts.

The required enamide **4a** was synthesized from the Baylis–Hillman adduct of 2-bromobenzaldehyde **1a** by following the sequential reactions: (1) acetylation of **1a** with Ac_2O in the presence of DMAP (96%), (2) S_N2' reaction with NaN_3 in DMSO (72%), (3) Staudinger reaction with PPh_3 in aq THF to prepare **2a** (88%), and (4) the reaction with 2-acetylbenzoic acid (**3a**) in toluene to synthesize enamide **4a** in moderate yield (Scheme 1).[3a] With this compound **4a** in our hands we examined the cyclization under typical radical cyclization reaction conditions using *n*-Bu_3SnH/AIBN in benzene.[4] We obtained tricyclic dihydropyrido[2,1-*a*] isoindolone compound **5a** in 56% yield, unexpectedly.[4,5] We did not observe the other meaningful spots on TLC



Scheme 2.



4f (47%) **8** (58%)

Scheme 3.

although many intractable spots were found. In order to check the possibility for the formation of eight-membered compound **6**[6] or seven-membered compound **7**,[3a,b] we examined the reaction conditions including reaction temperature and the amount of *n*-Bu_3SnH; however, we could not detect nor isolate any new compounds in appreciable amounts.

The structure of compound **5a** was confirmed by IR, ^1H and ^{13}C NMR, mass, and eventually by its X-ray crystallographic structure (Fig. 1).[4,7] Compound **5a** might be produced via the proposed mechanism in Scheme 2. The intermediate benzylic radical (**III**) could be generated from the initially generated aryl radical (**I**) by successive 1,5-hydrogen atom abstraction[8] to form the intermediate (**II**) and conversion to benzylic radical (**III**). It is interesting to note that the aryl radical (**I**) has allylic protons at 1,5-position thus translocation of aryl radical to the more stable allyl radical (**II**) occurred easily. Radical cyclization of this benzylic radical (**III**) in a 6-*endo*-*trig* manner and the hydrogen atom abstraction from *n*-Bu_3SnH furnished **5a**.

We examined the generality of this reaction by using enamides **4b–e** and we obtained the expected tricyclic compounds **5b–e** in 46–63% yields (Table 1). As shown in entries 4 and 5 benzylidene derivatives **4d** and **4e** showed similar reactivity to produce **5d** and **5e**, respectively. However, we did not obtain **5a** from the reaction of chloro derivative **4f**. Instead we isolated the reduction compound **8** in 58% yield (Scheme 3).[9]

In summary, we disclosed the synthesis of dihydropyrido[2,1-*a*]isoindolone derivatives from the radical cyclization reaction of enamide derivatives, which were synthesized in 4 steps from the Baylis–Hillman adducts of *ortho*-bromobenzaldehydes.

Acknowledgments

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, KRF-2006-311-C00384). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

References and notes

1. For the review articles on Baylis–Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp 201–350; (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062; (d) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645; (e) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490, and further references cited therein.
2. For the examples of radical cyclization reactions involving Baylis–Hillman adducts, see: (a) Gowrisankar, S.; Lee, K. Y.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 5785–5788; (b) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 4052–4058; (c) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859–4863; (d) Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1440–1442; (e) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 929–932; (f) Gowrisankar, S.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 2097–2100; (g) Majhi, T. P.; Neogi, A.; Ghosh, S.; Mukherjee, A. K.; Chattopadhyay, P. *Tetrahedron* **2006**, *62*, 12003–12010; (h) Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett.* **2005**, *46*, 3369–3372; (i) Shanmugam, P.; Rajasingh, P. *Tetrahedron* **2004**, *60*, 9283–9295; (j) Shanmugam, P.; Rajasingh, P. *Synlett* **2005**, 939–942.
3. For the synthesis and radical cyclizations of enamides, see: (a) Cid, M. M.; Dominguez, D.; Castedo, L.; Vazquez-Lopez, E. M. *Tetrahedron* **1999**, *55*, 5599–5610; (b) Rodriguez, G.; Cid, M. M.; Saa, C.; Castedo, L.; Dominguez, D. *J. Org. Chem.* **1996**, *61*, 2780–2782; (c) Ishibashi, H.; Kato, I.; Takeda, Y.; Kogure, M.; Tamura, O. *Chem. Commun.* **2000**, 1527–1528; (d) Guerrero, M. A.; Cruz-Almanza, R.; Miranda, L. D. *Tetrahedron* **2003**, *59*, 4953–4958; (e) Kato, I.; Higashimoto, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 7983–7989; (f) Zhou, A.; Njogu, M. N.; Pittman, C. U., Jr. *Tetrahedron* **2006**, *62*, 4093–4102.
4. Typical procedure for the synthesis of **5a** and the spectroscopic data of **4a** and **5a–e** are as follows: A stirred mixture of **4a** (165 mg, 0.4 mmol), *n*-Bu_3SnH (175 mg, 0.6 mmol), AIBN (13 mg, 0.08 mmol) in benzene (5 mL) was heated to reflux for 3 h. After usual aqueous workup procedure and column chromatographic purification process (hexanes/EtOAc, 6:4), we obtained **5a** as a white solid, 75 mg (56%). Compound **4a**: 41%; colorless oil; IR (KBr) 2981, 1718, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, $J = 7.5$ Hz, 3H), 4.21 (q, $J = 7.5$ Hz, 2H), 4.62 (d, $J = 2.5$ Hz, 1H), 4.83 (d, $J = 1.5$ Hz, 2H), 5.07 (d, $J = 2.5$ Hz, 1H), 7.05–7.09 (m, 1H), 7.21–7.24 (m, 1H), 7.27–7.30 (m, 1H), 7.40–7.44 (m, 1H), 7.48–7.56 (m, 3H), 7.71–7.74 (m, 1H), 7.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.00, 36.95, 61.24, 90.17, 119.51, 122.95, 123.24, 127.05, 128.89, 129.16, 129.41, 129.86, 130.43, 131.78, 132.54, 134.84, 136.12, 140.81, 141.11, 166.13, 166.78; LCMS *m/z* 411 (M^+). Anal. Calcd for $C_{21}H_{18}BrNO_3$: C, 61.18; H, 4.40; N, 3.40. Found: C, 61.32; H, 4.51; N, 3.97. Compound **5a**: 56%; white solid, mp 195–198 °C; IR (KBr) 2925, 1714, 1626, 1261 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, $J = 7.0$ Hz, 3H), 1.57–1.65 (m, 1H), 2.81–2.86 (m, 1H), 3.94–4.00 (m, 1H), 4.02–4.08 (m, 2H), 4.75 (dd, $J = 12.5$ and 2.5 Hz, 1H), 7.16–7.28 (m, 5H), 7.46 (d, $J = 7.5$ Hz,

1H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 8.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.90, 38.11, 41.12, 57.12, 60.04, 115.50, 122.23, 124.57, 126.42, 126.73, 128.50, 128.94, 131.17, 131.80, 133.07, 144.10, 144.22, 165.45, 166.21; LCMS m/z 333 (M^+). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.45; H, 5.87; N, 4.03.

Compound **5b**: 56%; white solid, mp 189–191 °C; IR (KBr) 2925, 1714, 1261 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62–1.64 (m, 1H), 2.80–2.84 (m, 1H), 3.57 (s, 3H), 4.02–4.08 (m, 1H), 4.73–4.78 (m, 1H), 7.16–7.31(m, 5H), 7.45–7.65 (m, 3H), 7.94 (d, $J = 7.5$ Hz, 1H), 8.36 (d, $J = 1.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.20, 41.11, 51.31, 57.12, 115.17, 122.28, 124.67, 126.55, 126.73, 128.61, 129.02, 131.23, 132.10, 133.15, 143.98, 144.26, 165.49, 166.61; LCMS m/z 319 (M^+). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.09; H, 5.56; N, 4.36.

Compound **5c**: 63%; white solid, mp 193–195 °C; IR (KBr) 2950, 1712, 1275 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52–1.64 (m, 1H), 2.80–2.88 (m, 1H), 3.59 (s, 3H), 4.02–4.11 (m, 1H), 4.72–4.77 (m, 1H), 6.86–6.88 (m, 2H), 6.94–6.97 (m, 1H), 7.20–7.27 (m, 1H), 7.46–7.55 (m, 2H), 7.61–7.66 (m, 1H), 7.93 (d, $J = 7.5$ Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.93, 40.79, 51.32, 56.90, 113.28, 113.53, 113.56, 113.82, 114.31, 122.28, 122.33, 122.37, 124.66, 129.06, 129.98, 130.08, 131.09, 132.46, 133.21, 144.07, 146.59, 146.68, 161.27, 164.53, 165.39, 166.38. Anal. Calcd for $C_{20}H_{16}FNO_3$: C, 71.21; H, 4.78; N, 4.15. Found: C, 71.13; H, 4.97; N, 4.38.

Compound **5d**: 46%; white solid, mp 200–202 °C; IR (KBr) 2909, 1714, 1263 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, $J = 6.9$ Hz, 3H), 3.94–4.16 (m, 3H), 4.62 (dd, $J = 2.4$ Hz, 1H), 5.24 (d, $J = 3.6$ Hz, 1H), 6.62 (s, 2H), 6.81–6.82 (m, 5H), 6.96–6.98 (m, 3H), 7.18–7.45 (m, 3H), 7.74 (d, $J = 7.8$ Hz, 1H), 8.47 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.90, 45.63, 48.32, 60.25, 60.78, 115.21, 122.58, 124.28, 125.84, 126.71, 127.50, 127.77, 128.51, 131.41, 132.14, 132.78, 135.40, 140.71, 143.19, 166.97, 166.68 (two aromatic carbons were overlapped); LCMS m/z 409 (M^+).

Compound **5e**: 49%; white solid, mp 211–213 °C; IR (KBr) 2950, 1714, 1397 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.95 (dd, $J = 3.9$ Hz, 1H), 4.62 (dd, $J = 2.3$ Hz, 1H), 5.25 (d, $J = 3.9$ Hz, 1H), 6.61 (s, 2H), 6.80–6.81 (m, 5H), 6.93–7.00 (m, 3H), 7.26–7.46 (m, 3H), 7.74 (d, $J = 7.8$ Hz, 1H), 8.48 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.52, 48.36, 51.44, 60.72, 114.75, 122.59, 124.29, 125.89, 126.72, 127.54, 127.70, 127.76, 128.53, 131.36, 132.45, 132.82, 135.44, 140.52, 143.20, 165.98, 167.04 (one aromatic carbon was overlapped). Anal. Calcd for $C_{26}H_{21}NO_3$: C, 78.97; H, 5.35; N, 3.54. Found: C, 78.65; H, 5.37; N, 3.39.

5. For the synthesis of similar pyridoisoindole derivatives, see: (a) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095–5097; (b) Ha, D.-C.; Yun, C.-S.; Yu, E. *Tetrahedron Lett.* **1996**, *37*, 2577–2580; (c) Othman, M.; Pigeon, P.; Decroix, B. *Tetrahedron* **1998**, *54*, 8737–8744; (d) Mangeney, P.; Pays, C. *Tetrahedron Lett.* **2003**, *44*, 5719–5722; (e) Pays, C.; Mangeney, P. *Tetrahedron Lett.* **2001**, *42*, 589–592; (f) Zhang, W.; Zheng, A.; Liu, Z.; Yang, L.; Liu, Z. *Tetrahedron Lett.* **2005**, *46*, 5691–5694; (g) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009–3018; (h) Varlamov, A. V.; Zubkov, F. I.; Boltukhina, E. V.; Sidorenko, N. V.; Borisov, R. S. *Tetrahedron Lett.* **2003**, *44*, 3641–3643.

6. For the synthesis of eight-membered ring compounds via radical cyclizations, see: (a) Bremner, J. B.; Sengpracha, W. *Tetrahedron* **2005**, *61*, 941–953; (b) Lee, E.; Yoon, C. H.; Lee, T. H.; Kim, S. Y.; Ha, T. J.; Sung, Y.-S.; Park, S.-H.; Lee, S. *J. Am. Chem. Soc.* **1998**, *120*, 7469–7478; (c) Lang, S.; Corr, M.; Muir, N.; Khan, T. A.; Schonebeck, F.; Murphy, J. A.; Payne, A. H.; Williams, A. C. *Tetrahedron Lett.* **2005**, *46*, 4027–4030; (d) Kaim, L. E.; Grimaud, L.; Miranda, L. D.; Vieu, E. *Tetrahedron Lett.* **2006**, *47*, 8259–8261.

7. Crystal data of compound **5a**: solvent of crystal growth (hexanes/CH_2Cl_2, 95:5); empirical formula $C_{21}H_{19}NO_3$, $Fw = 333.37$, crystal dimensions $0.60 \times 0.20 \times 0.02$ mm^3, monoclinic, space group $P2(1)/c$, $a = 17.9110(19)$ Å, $b = 6.3191(7)$ Å, $c = 15.3166(17)$ Å, $\alpha = 90°$, $\beta = 94.424(2)°$, $\gamma = 90°$, $V = 1728.4(3)$ Å^3, $Z = 4$, $D_{calcd} = 1.281$ mg/m^3. $F_{000} = 704$, MoKα ($\lambda = 0.71073$ Å), $R_1 = 0.0747$, $wR_2 = 0.1718$ ($I > 2\sigma(I)$). We omitted hydrogen atoms for clarity (Fig. 1). The X-ray data has been deposited in CCDC with number 634382.

8. For the examples of intramolecular hydrogen transfer of radical intermediates, see: (a) Dort, P. C. V.; Fuchs, P. L. *J. Org. Chem.* **1997**, *62*, 7142–7147; (b) Curran, D. P.; Yang, F.; Cheong, J.-H. *J. Am. Chem. Soc.* **2002**, *124*, 14993–15000; (c) Zeng, L.; Kaoudi, T.; Schiesser, C. H. *Tetrahedron Lett.* **2006**, *47*, 7911–7914; (d) Rancourt, J.; Gorys, V.; Jolicoeur, E. *Tetrahedron Lett.* **1998**, *39*, 5339–5342; (e) Amrein, S.; Bossart, M.; Vasella, T.; Studer, A. *J. Org. Chem.* **2000**, *65*, 4218–4288; (f) Qian, X.; Cui, J.; Zhang, R. *Chem. Commun.* **2001**, 2656–2657; (g) Karady, S.; Cummins, J. M.; Dannenberg, J. J.; del Rio, E.; Dormer, P. G.; Marcune, B. F.; Reamer, R. A.; Sordo, T. L. *Org. Lett.* **2003**, *5*, 1175–1178; (h) Renaud, P.; Beaufils, F.; Feray, L.; Schenk, K. *Angew. Chem.* **2003**, *115*, 4362–4365; (i) Clive, D. L. J.; Yang, W.; MacDonald, A. C.; Wang, Z.; Cantin, M. *J. Org. Chem.* **2001**, *66*, 1966–1983.

9. The formation of compound **8** from **4f** clearly stated that the corresponding aryl radical must be generated in the reaction. However, we could not explain the different reactivity of two aryl radicals generated from **4a** and **4f** at this stage.