Tetrahedron Letters 53 (2012) 4828–4831

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

DABCO-mediated one-pot sequential transformation: convenient access to fluorinated 1*H*-pyrazol-5(4*H*)-ones

Jun-Wei Wu, Feng Li, Yan Zheng, Jing Nie *

Department of Chemistry, Tianjin University, Tianjin 300072, China

ARTICLE INFO

Article history:
Received 9 May 2012
Revised 14 June 2012
Accepted 26 June 2012
Available online 29 June 2012

Keywords:
Pyrazolones
Allylic alkylation
Electrophilic fluorination
One-pot sequential transformation
Synthesis

ABSTRACT

A Lewis base-mediated one-pot sequential transformation of pyrazolones with Morita-Baylis-Hillman (MBH) carbonates and *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (NFSI) has been developed. By using this process, a series of fluorinated pyrazolone derivatives have been synthesized in 40–83% yields.

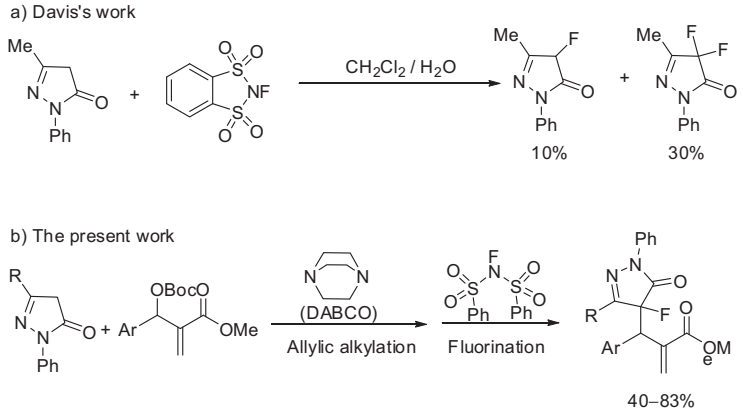
The efficient assembly of densely functionalized fluorinated heterocycles is an appealing subject of investigation due to their wide application in pharmaceuticals, agrochemicals, and new materials.[1] Among synthetic routes to these compounds, one-pot multistep transformation appears to be a powerful method for creating structural diversity by virtue of avoiding the monotonous purification of intermediate.[2] In this aspect, a great deal of efforts has been devoted to the designing of highly selective and efficient one-pot multistep transformations in accord with the increasing need for the continued advancement of the field of organofluorine chemistry.[3] Despite the remarkable achievement made in this area, the employment of one-pot strategy from readily available precursors for rapid and efficient construction of fluorinated aza-heterocyclic compounds is still in great demand.

Pyrazolone, an important class of aza-heterocycles, represents a prominent structural subunit present in numerous biologically active compounds, such as analgesic and antipyretic properties.[4] During the past decades, the usefulness of pyrazolones as nucleophiles has been explored for construction of a variety of pyrazolone derivatives.[5] However, the use and preparation of monofluorinated pyrazolones is extremely rare. Only one report by Davis and co-workers has addressed the electrophilic fluorination of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one with *N*-fluoro-*o*-benzenedisulfonimide, but a mixture of mono- and difluorinated products was obtained in low yield (Scheme 1a).[6] We surmised that a sequential allylic alkylation/electrophilic fluorination in one-pot could provide an alternative method for the preparation of monofluorinated pyrazolone derivatives. Moreno-Manas and co-workers once described an allylation reaction of pyrazolones with acrylic esters to afford the mixture of *C*-, *N*-, and di-allylated products,[7a] whereas Grigg and co-workers presented a Pd(0)-catalyzed cascade transformation of an iodide and allene with pyrazolin-5-one to give the di-allylated pyrazolones.[7b] As a part of our ongoing interest in developing innovative methodologies for the preparation of fluorinated compounds,[3d-f] we recently found that 1,4-diazabicyclo[2.2.2]octane (DABCO) can catalyze the allylic alkylation of 1*H*-pyrazol-5(4*H*)-ones with Morita-Baylis-Hillman (MBH) carbonates,[8] to afford allylated pyrazolones, which could be further converted into monofluorinated products through one-pot sequential transformation (Scheme 1b). In this communication, we report our preliminary results on this subject.

To validate our hypothesis, the model reaction of MBH carbonate **1a** and 3-methyl-1-phenylpyrazol-5-one **2a** was performed in the presence of 20 mol % of DABCO in toluene at room temperature. As indicated in Table 1, the allylation reaction proceeded well, affording pyrazol-5-ol Int-**A** in 67% yield. The regioisomer Int-**B** was also formed in 21% yield (entry 1). Screening of the Lewis bases revealed that the use of DABCO allowed for the best regioselectivity of this allylic substitution (entries 1–4). Further optimization on the other reaction conditions (including solvent and base's loading) led to the discovery that the regioisomer of Int-**A** was formed exclusively in 89% yield when toluene was used as solvent and base's loading was increased to 150 mol % (entry 7). Based on these results, the one-pot procedure was next attempted by employing NFSI as electrophilic fluorinating reagent for synthesis

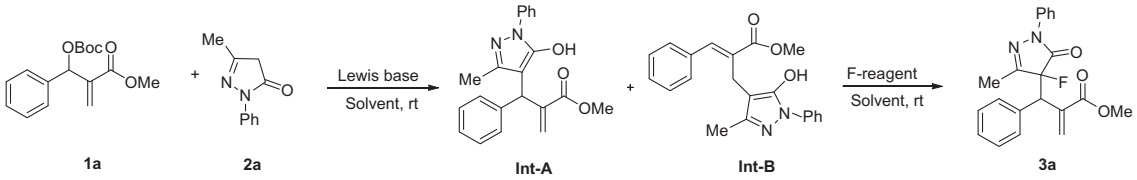
* Corresponding author.
E-mail address: niejing@tju.edu.cn (J. Nie).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.06.110



Scheme 1. Synthesis of fluorinated pyrazolones.

Table 1
Optimization of the conditions for the one-pot synthesis of **3a**[a]



Entry	Lewis base (mol %)	Solvent	F-reagent	Yield[b] (%)		
				Int-A	Int-B	**3a**[d]
1	DABCO (20)	Toluene	—	67	21	—
2	DMAP (20)	Toluene	—	56	24	—
3	DBU (20)	Toluene	—	51	23	—
4	PPh_3 (20)	Toluene	—	60	30	—
5	DABCO (50)	Toluene	—	78	8	—
6	DABCO (100)	Toluene	—	85	—	—
7	DABCO (150)	Toluene	—	89	—	—
8	DABCO (150)	Toluene	NFSI	12	—	63
9	DABCO (150)	Toluene	Selectfluor	55	—	10
10	DABCO (150)	CH_2Cl_2	NFSI	10	7	55
11	DABCO (150)	DCE	NFSI	13	7	51
12	DABCO (150)	THF	NFSI	20	5	46
13[c]	DABCO (150)	Toluene	NFSI	22	9	41

[a] **1a**/**2a**/Base/F-reagent = 1.5/1/1.5/1.5 in 2 mL of solvents.
[b] Isolated yield.
[c] The reaction was performed at 40 °C.
[d] The dr value (50/50−75/25) was determined by ^{19}F NMR of the crude product.

of fluorinated compound. Gratifyingly, the desired fluorinated product of **3a** was isolated in 63% yield as single regioisomer, albeit with moderate diastereoselectivity (72/28 dr). Subsequent change of the electrophilic fluorinating reagent to selectfluor resulted in the dramatically diminished yield of **3a** (entry 9). A sharp decrease of yield was observed as raising reaction temperature to 40 °C (entry 13). Overall, the optimized conditions for the fluorination step were using NFSI as fluorinated reagent in toluene at room temperature.

Under the optimized experimental conditions, the scope of the one-pot multistep transformation for synthesis of **3** was examined with a variety of MBH carbonates **1** and pyrazolones **2**, and the results are summarized in Table 2.[9] It was found that when MBH carbonates with electron-withdrawing or -donating groups on aromatic rings were used, the one-pot transformations proceeded smoothly to give **3a–l** in 40–83% yields with acceptable diastereoselectivities (from 50/50 to 80/20 dr). However, the relatively lower yields were observed within the MBH carbonates **1** bearing functional group at the 2-position of aromatic ring (40% yield, entry 7). Moreover, the reactions with 1- and 2-naphthyl pyrazolones were uneventful, and furnished the fluorinated pyrazolones **3j** and **3k**, respectively (entries 10 and 11). Notably, heteroaromatic substrate was also viable substrates, affording the desired product **3l** in 65% yield with 85/15 dr (entry 12). Next, a number of 3-substituted pyrazolones have also been explored in this one-pot multistep reaction. 52–64% yields were obtained for pyrazolones bearing electron-neutral or -rich or -deficient aryl groups (entries 13–16).

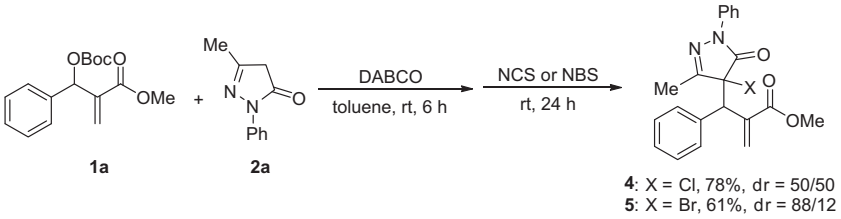
To test the synthetic potential of the present approach, we extended this one-pot methodology to electrophilic chlorinating and brominating reagents. It was found that in the presence of DABCO, the reaction of MBH carbonates **1a** and pyrazol-5-one **2a** with NCS and NBS delivered the corresponding chlorinated and brominated pyrazolones **4** and **5** in 78% and 61% yields, respectively (Scheme 2).[10]

On the basis of above experimental results and previous work, a plausible mechanism accounting for the formation of **3** is illustrated in Scheme 3. DABCO attacks from the β′-position of MBH

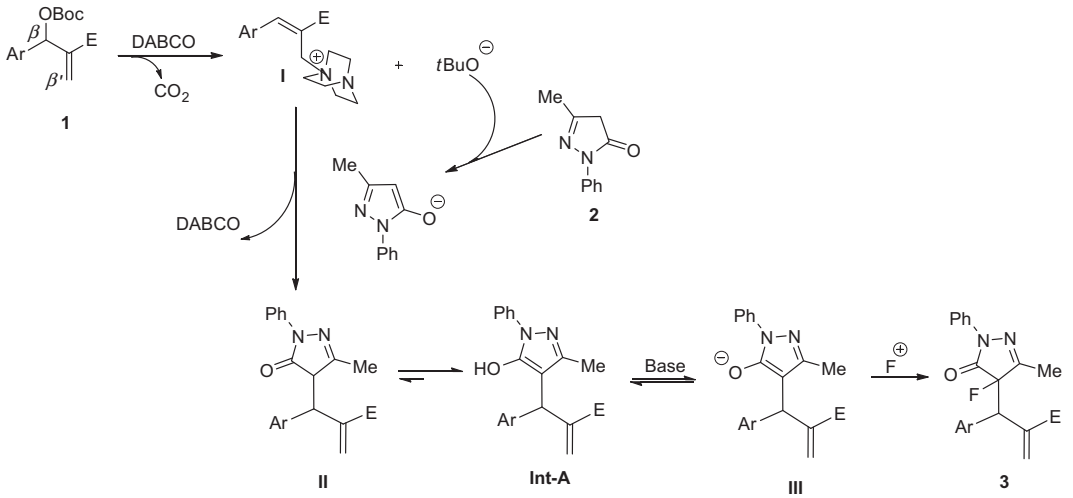
Table 2
Substrate scope for one-pot synthesis of **3**[a]

Entry	Ar	R	Product **3**	Yield[b] (%)	Dr[c]
1	Ph	Me	**3a**	63	72/28
2	4-MeC_6H_4	Me	**3b**	58	78/22
3	4-$MeOC_6H_4$	Me	**3c**	53	80/20
4	4-FC_6H_4	Me	**3d**	61	78/22
5	4-ClC_6H_4	Me	**3e**	73	75/25
6	4-BrC_6H_4	Me	**3f**	80	71/29
7	2-BrC_6H_4	Me	**3g**	40	60/40
8	3-$MeOC_6H_4$	Me	**3h**	62	80/20
9	3,4-$Cl_2C_6H_3$	Me	**3i**	83	67/33
10	1-Naphthyl	Me	**3j**	54	50/50
11	2-Naphthyl	Me	**3k**	75	70/30
12	2-Furanyl	Me	**3l**	65	85/15
13	Ph	Ph	**3m**	59	60/40
14	Ph	4-$MeOC_6H_4$	**3n**	52	65/35
15	Ph	4-ClC_6H_4	**3o**	61	70/30
16	Ph	4-BrC_6H_4	**3p**	64	73/27

[a] **1**/**2**/Base/F-reagent = 1.5/1/1.5/1.5 in 2 mL of toluene.
[b] Isolated yield.
[c] The dr value was determined by ^{19}F NMR of the crude product.



Scheme 2. One-pot synthesis of **4** and **5**.



Scheme 3. Plausible mechanism for the formation of fluorinated pyrazolones **3**.

carbonate to form a quaternary ammonium ion I. The deprotonation of pyrazolone at C-4 by in situ generated *tert*-butoxide anion occurs, and is followed by allylation of I to give intermediate II along with elimination of DABCO. It should be pointed out that pyrazol-5-ones in this allylations mainly exist as OH-tautomeric forms Int-**A**, which have been verified by ^1H NMR analysis.[11]

Finally, the resulting enolate III derived from deprotonation of Int-**A** is captured by electrophilic fluorinating reagent to furnish the corresponding fluorinated compound **3**.

In summary, we have developed a one-pot sequential allylic alkylation/electrophilic fluorination transformation for the facile synthesis of fluorinated allylic pyrazolones. A series of fluorinated pyrazolone derivatives were obtained in moderate to good yields. In the presence of NBS and NCS, further extension of this one-pot sequential protocol also proved effective. The development of catalytic enantioselective systems, as well as the application of this process to the synthesis of bioactive fluorinated compounds are ongoing in our laboratory and will be reported in due course.

Acknowledgment

The financial support from the National Natural Science Foundation of China (NSFC) (No. 20972110 and 21002068) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.110.

References and notes

1. For recent reviews, see: (a) Zhu, S. Z.; Wang, Y.; Peng, W.; Song, L. P.; Jin, G. F. *Curr. Org. Chem.* **2002**, *6*, 1057; (b) He, P.; Zhu, S. Z. *Mini-Rev. Org. Chem.* **2004**, *1*, 417; (c) Special issue on "fluorine in the life sciences". *ChemBioChem* **2004**, *5*, 557.; (d) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, UK, 2004; (e) Meng, W.-D.; Qing, F.-L. *Curr. Top. Med. Chem.* **2006**, *6*, 1499; (f) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303; (g) Sandford, G. *J. Fluorine Chem.* **2007**, *128*, 90; (h) Kirk, K. L. *Org. Process. Res. Dev.* **2008**, *12*, 305; (i) Purser, S.; Moore, P. R.; Swallowb, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
2. For recent reviews, see: (a) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551; (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 9456; (c) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302; (d) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001; (e) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (f) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 354; (g) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354; (h) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570; (i) Tietze, L. F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367; (j) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492; (k) Climent, M. J.; Corma, A.; Iborra, S. *Chem. Rev.* **2011**, *111*, 1072.
3. For recent reviews, see: (a) Wilkinson, S. C.; Salmon, R.; Gouverneur, V. *Future Med. Chem.* **2009**, *1*, 847; (b) Zhu, S. Z.; Song, L. P.; Jin, G. F.; Dai, B. F.; Hao, J. *Curr. Org. Chem.* **2009**, *13*, 1015; For selected recent examples, see: (c) Lourie, L. F.; Serguchev, Y. A.; Shevchenko, G. V.; Ponomarenko, M. V.; Chernega, A. N.; Rusanov, E. B.; Howard, J. A. K. *J. Fluorine Chem.* **2006**, *127*, 377; (d) Cui, H.-F.; Dong, K.-Y.; Zhang, G.-W.; Wang, L.; Ma, J.-A. *Chem. Commun.* **2007**, 2284; (e) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053; (f) Li, F.; Nie, J.; Wu, J.-W.; Zheng, Y.; Ma, J.-A. *J. Org. Chem.* **2012**, *77*, 2398; (g) Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2008**, 3876; (h) Zhou, C.; Ma, Z.; Gu, Z.; Fu, C.; Ma, S. *J. Org. Chem.* **2008**, *73*, 772; (i) Rudler, H.; Parlier, A.; Hamon, L.; Herson, P.; Daran, J.-C. *Chem. Commun.* **2008**, 4150; (j) Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 7927; (k) Cui, H.; Li, P.; Chai, Z.; Zheng, C.; Zhao, G.; Zhu, S. *J. Org. Chem.* **2009**, *74*, 1400; (l) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354; (m) Kishi, Y.; Inagi, S.; Fuchigami, T. *Eur. J. Org. Chem.* **2009**, 103; (n) Wang, H.-F.; Cui, H.-F.; Chai, Z.; Li, P.; Zheng, C.-W.; Yang, Y.-Q.; Zhang, G. *Chem. Eur. J.* **2009**, *15*, 13299; (o) Wilinson, S. C.; Lozano, O.; Schuler, M.; Pacheco, M. C.; Salmon, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 7083; (p) Cui, H.-F.; Yang, Y.-Q.; Chai, Z.; Li, P.; Zhang, C.-W.; Zhu, S.-Z.; Zhao, G. *J. Org. Chem.* **2010**, *75*, 117; (q) Lozano, O.; Blessley, G.; Campo, T. M.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 8105; (r) Lin, R.; Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2011**, *13*, 4498; (s) Xu, T.; Mu, X.; Peng, H.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 8176.
4. For reviews on pyrazolines, see: (a) Lévai, A. *J. Heterocycl. Chem.* **2002**, *39*, 1; (b) Kumar, S.; Bawa, S.; Drahu, S.; Kumar, R.; Gupta, H. *Recent Pat. Anticancer Drug Discov.* **2009**, *4*, 154; (c) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev.* **2010**, *39*, 845; (d) Küchenthal, C.-H.; Maison, W. *Synthesis* **2010**, *5*, 719.
5. For selected examples, see: (a) Boeckman, R. K., Jr; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 3651; (b) Abass, M.; Mostafa, B. B. *Bioorg. Med. Chem.* **2005**, *13*, 6133; (c) Chande, M. S.; Barve, P. A.; Suryanarayan, V. *J. Heterocycl. Chem.* **2007**, *44*, 49; (d) Mariappan, G.; Saha, B. P.; Bhuyan, N. R.; Bharti, P. R.; Kumar, D. *J. Adv. Pharm. Technol. Res.* **2010**, *1*, 260; (e) Ma, R.; Zhu, J.; Liu, J.; Chen, L.; Shen, X.; Jiang, H.; Li, J. *Molecules* **2010**, *15*, 3593; (f) Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2010**, *352*, 827; (g) Gogoi, S.; Zhao, C.-G. *Tetrahedron Lett.* **2009**, *50*, 2252; (h) Radi, M.; Bernardo, V.; Bechi, B.; Castagnolo, D.; Pagano, M.; Botta, M. *Tetrahedron Lett.* **2009**, *50*, 6572; (i) Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249; (j) Yang, Z. G.; Wang, Z.; Bai, S.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 596; (k) Alba, A. N.; Zea, A.; Valero, G.; Calbet, T.; Font-Bardía, M.; Mazzanti, A.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2011**, 1318; (l) Wang, Z.; Yang, Z.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 4928.
6. Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730.
7. (a) Moreno-Manas, M.; Pérez, M.; Pleixats, R. *Tetrahedron* **1994**, *50*, 515; (b) Grigg, R.; Sarkar, M. R. A.; Thayaparan, A.; Sridharan, V.; Fishwick, C. W. G. *Tetrahedron* **2007**, *63*, 7213.
8. For selected examples about MBH carbonates, see: (a) Basavarath, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001; (b) Ciganek, E. *Org. React.* **1997**, *51*, 201; For selected examples about MBH carbonates, see: (c) Du, Y.; Han, X.; Lu, X. *Tetrahedron* **2004**, *45*, 4967; (d) Zhang, T.-Z.; Dai, L.-X.; Hou, X.-L. *Tetrahedron: Asymmetry* **2007**, *18*, 1990; (e) van Steenis, D. J. V. C.; Marcelli, T.; Lutz, M.; Spek, A. L.; van Maarseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal.* **2007**, *349*, 281; (f) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202; (g) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737; (h) Zhang, S.-J.; Cui, H.-L.; Jiang, K.; Li, R.; Ding, Z.-Y.; Chen, Y.-C. *Eur. J. Org. Chem.* **2009**, 5804; (i) Cui, H.-L.; Peng, J.; Feng, X.; Du, W.; Jiang, K.; Chen, Y.-C. *Chem. Eur. J.* **2009**, *15*, 1574; (j) Sun, W.; Hong, L.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 3914; (k) Song, W.; Lei, M.; Shen, Y.; Cai, S.; Lu, W.; Lu, P.; Wang, Y. *Adv. Synth. Catal.* **2010**, *352*, 2432; (l) Zhou, R.; Wang, C.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 976; (m) Peng, J.; Huang, X.; Lei, H.-C.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 4260; (n) Furukawa, T.; Nishimine, T.; Tokunaga, E.; Hasegawa, K.; Shiro, M.; Shibata, N. *Org. Lett.* **2011**, *13*, 3972; (o) Jiang, L.; Lei, Q.; Huang, X.; Cui, H.-L.; Zhou, X.; Chen, Y.-C. *Chem. Eur. J.* **2011**, *17*, 9489; (p) Pei, C.-K.; Zhang, X.-C.; Shi, M. *Eur. J. Org. Chem.* **2011**, 4479; (q) Liu, H.; Yan, L.; Huang, K.-W.; Jiang, Z.; Tan, C.-H. *Chem. Eur. J.* **2011**, *17*, 8066.
9. *General procedure for one-pot synthesis of fluorinated products* **3**: MBH carbonate (0.15 mmol), pyrazolin-5-one (0.1 mmol), and DABCO (0.15 mmol), were added to a 10 mL schlenk equipped with a magneton. The vial was refilled with Ar for three times. Toluene (2 mL) was added and the resulting mixture was stirred at room temperature under Ar atmosphere for the appropriate time (2–6 h) until pyrazolin-5-one was consumed (monitored by TLC). Then NFSI (0.15 mmol) was added and the mixture was stirred at the same temperature for 24 h (monitored by TLC). The reaction solution was concentrated in vacuo and the crude was purified by flash chromatography with ethyl acetate/hexane (1/20, v/v) to afford the halogenated product **3**.
Compound **3a:** Yellow oil (23 mg, 63% yield, 72:28 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (d, J = 1.5 Hz, 3H), 3.73 (s, 3H), 4.92 (d, J = 10.6 Hz, 1H), 6.53 (s, 1H), 6.68 (s, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.30 (s, 1H), 7.32−7.43 (m, 6H), 7.61 (s, 1H), 7.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (d, $^2J_{C-F}$ = 21.2 Hz), 166.7, 156.7 (d, $^2J_{C-F}$ = 16.4 Hz), 136.9, 134.7, 133.0, 129.9, 129.4, 128.8, 128.6, 128.5, 125.7, 119.1, 94.6 (d, $^1J_{C-F}$ = 197.9 Hz), 52.3, 48.4 (d, $^2J_{C-F}$ = 24.6 Hz), 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −165.59 (d, J = 10.5 Hz); IR (KBr) ν 3064, 2954, 2924, 1728, 1498, 1367, 1253, 1151, 962, 820, 753, 704 cm^{-1}; MS (ESI) found: m/z = 755.0 [2M+Na]$^+$; HRMS (ESI) found: m/z 389.1271 [M+Na]$^+$, Anal. calcd. for $C_{21}H_{19}FN_2O_3$+Na 389.1277.10.
10. Compound **4**: Yellow oil (30 mg, 78% yield, 50:50 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.72 (s, 3H), 4.88 (s, 1H), 6.77 (s, 1H), 6.91 (s, 1H), 7.36−7.40 (m, 6H), 7.67 (d, J = 7.8 Hz, 2H), 7.58 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 166.9, 157.9, 137.3, 135.8, 134.1, 130.7, 129.0, 128.7, 128.4, 128.2, 125.8, 119.1, 66.8, 52.4, 50.2, 13.9; IR (KBr) ν 3064, 2953, 2926, 2849, 1724, 1596, 1498, 1365, 1274, 1148, 970, 825, 755, 703, 643 cm^{-1}; MS (ESI) found: m/z = 786.2 [2M+Na]$^+$; HRMS (ESI) found: m/z 405.0978 [M+Na]$^+$, Anal. calcd. for $C_{21}H_{19}ClN_2O_3$+Na 405.0982.
Compound **5**: Yellow oil (26 mg, 61% yield, 88:12 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.73 (s, 3H), 4.89 (s, 1H), 6.75 (s, 1H), 6.88 (s, 1H), 7.20−7.22 (m, 1H), 7.26−7.28 (m, 2H), 7.36−7.39 (m, 5H), 7.70 (d, J = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 166.9, 157.9, 137.2, 136.7, 134.4, 130.6, 129.3, 128.9, 128.7, 128.5, 125.8, 119.5, 58.0, 52.4, 49.8, 14.2; IR (KBr) ν 3063, 2952, 2852, 1719, 1595, 1497, 1364, 1271, 1149, 972, 820, 755, 704, 624 cm^{-1}; MS (ESI) found: m/z = 444.8 [M+NH$_4$]$^+$; HRMS (ESI) found: m/z 449.0469 [M+Na]$^+$, Anal. calcd. for $C_{21}H_{19}BrN_2O_3$+Na 449.0477.
11. Spectral data of Int-**A**: ^{1}H NMR (400 MHz, [D_6]-DMSO) δ 1.89 (s, 3H), 3.65 (s, 3H), 5.18 (s, 1H) 5.46 (s, 1H), 6.33 (s, 1H), 7.19−7.25 (m, 4H), 7.29−7.31 (m, 2H), 7.41−7.44 (m, 2H), 7.75 (d, J = 7.2 Hz, 2H), 10.88 (s, 1H); ^{13}C NMR (100 MHz, [D_4]-MeOH) δ 167.5, 147.6, 141.6, 140.9, 128.8, 128.5, 128.3, 128.0, 127.8, 126.3, 126.0, 125.9, 124.9, 120.7, 51.1, 22.3, 13.0; IR (KBr) ν 3063, 2924, 2853, 1721, 1596, 1498, 1366, 1259, 1149, 965, 756, 703 cm^{-1}; MS (ESI) found: m/z = 349.6[M+H]$^+$; HRMS (ESI) found: m/z 371.1366 [M+Na]$^+$, Anal. calcd. for $C_{21}H_{20}N_2O_3$+Na 371.1372.