Available online at www.sciencedirect.com
SCIENCE DIRECT®

Tetrahedron Letters 47 (2006) 2511–2514

Tetrahedron Letters

Rapid and convenient synthesis of aryl- and heteroaryl-α-hydroxy-α-trifluoromethyl acetate via Friedel–Crafts alkylation under solvent- and catalyst-free conditions

Jun-Ling Zhao, Li Liu,* Hai-Bo Zhang, Yan-Chao Wu, Dong Wang* and Yong Jun Chen*

Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China

Received 21 November 2005; revised 9 February 2006; accepted 10 February 2006

Abstract—Solvent- and catalyst-free Friedel–Crafts alkylation reactions of aromatic and heteroaromatic compounds with methyl trifluoropyruvate (**2**) were carried out at room temperature and finished in several minutes with good to excellent yields of the addition products (69→99%), which provided a rapid and convenient method to synthesize aryl- and heteroaryl-α-hydroxy-α-triflouromethyl acetates.

Friedel–Crafts alkylation is one of the most important C–C bond forming reactions, which provides an efficient synthetic route to numerous functionalized aromatic compounds possessing special properties. Among the Friedel–Crafts alkylations, the addition reaction of aromatic and heteroaromatic compounds to carbonyl compounds has attracted considerable attention.[1] In general, the Friedel–Crafts alkylation reaction needs a proper catalyst, such as a protic acid,[2] Lewis acid[3] or organocatalyst,[4] as well as an organic solvent. Recently, solvent-free organic reaction has got noticeable progress.[5] In the view of the principle of green chemistry,[6] a 'clean' synthesis should be a desirable without using any solvent and catalyst. On the other hand, organofluorine compounds, especially trifluoromethyl-substituted ones, are useful both in organic synthesis and the development of novel drugs.[7] For the synthesis of CF$_3$-substituted compounds, the Friedel–Crafts alkylation of aromatic compounds with trifluoropyruvate is a method of choice. It has been reported that the asymmetric addition of aromatics and heteroaromatics with trifluoropyruvate can be catalyzed by chiral Lewis acid[8] or organocatalyst.[4] Recently, Olah and co-workers[9] reported a superacid-catalyzed reaction of heteroaromatic or substituted benzene with trifluoropyruvate in suitable organic solvent and under inert atmosphere. We[10] also presented an In(OTf)$_3$-catalyzed Friedel–Crafts reaction of aromatic compounds in water and air atmosphere for the synthesis of Mosher acid analogues. As our continuous interest in the Friedel–Crafts alkylation, herein, we would like to report the Friedel–Crafts reaction of aromatic and heteroaromatic compounds with methyl trifluoropyruvate under solvent-free condition without using any catalyst or additives for the rapid and convenient synthesis of aryl- and heteroaryl-α-hydroxy-α-trifluoromethyl acetates.

At first, the reaction of *N*,*N*-dimethylaniline (**1a**) with methyl trifluoropyruvate (**2**) was performed at room temperature without the use of catalyst in various solvents (Scheme 1). As shown in Table 1, the addition product, *N*,*N*-dimethyl-4-(α-hydroxyl-α-carbomethoxy-trifluoroethyl)aniline (**3a**) was obtained in only moderate yields (0–67%) after 24 h in the presence of a solvent. Surprisingly, when **2** was added to neat **1a**, the reaction took place immediately and was completed within 4 min. The reaction gave an excellent yield of **3a** (96%) (Table 1, entry 7).

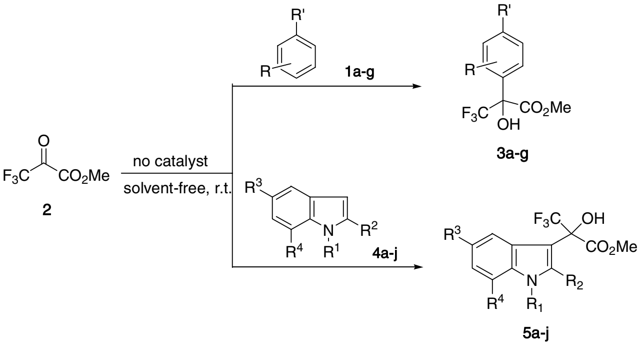
The results encouraged us to extend the scope of aromatic substrates. Various aniline derivatives **1a**–**i** were used in the solvent- and catalyst-free Friedel–Crafts alkylation with **2** at room temperature (Table 2).[11] In nearly all the cases, a remarkable acceleration effect

---

Keywords: Solvent- and catalyst-free; Friedel–Crafts alkylation; α-Hydroxy-α-trifluoromethyl carboxylate.

* Corresponding authors. Tel.: +86 10 6255 4614; fax: +86 10 6255 4449 (Y.J.C.); e-mail addresses: dwang210@iccas.ac.cn; yjchen@iccas.ac.cn

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.02.054



Scheme 1.

Table 1. Friedel–Crafts alkylations of **1a** or **4a** with **2** in various solvents[a]

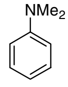
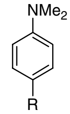
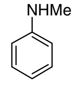
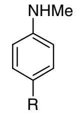
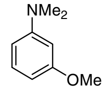
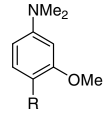
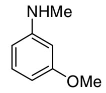
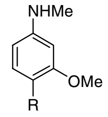
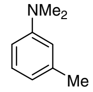
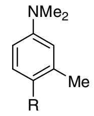
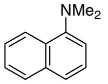
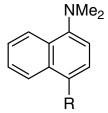
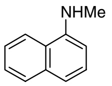
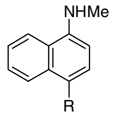
Entry	Ar–H	Solvent	Time	Yield[b] (%)
1	**1a**	CH_2Cl_2	24 h	60
2	**1a**	1,4-Dioxane	24 h	23
3	**1a**	CH_3OH	24 h	n.r.[c]
4	**1a**	Toluene	24 h	67
5	**1a**	DMSO	24 h	Trace
6	**1a**	Et_2O	24 h	28
7	**1a**	None	4 min	96
8	**4a**	Et_2O	90 h	95[4b]
9	**4a**	Toluene	24 h	96
10	**4a**	CH_2Cl_2	24 h	94
11	**4a**	None	1 min	96

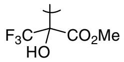
[a] At room temperature, without using catalyst.

[b] Isolated yield.

[c] Starting material recovered.

Table 2. Friedel–Crafts reactions of **1a**–**g** with **2** under solvent- and catalyst-free conditions

Entry	Ar–H	Time (min)	Product[a]	Yield[b] (%)
1	**1a** 	4	**3a** 	96
2	**1b** 	5	**3b** 	>99
3	**1c** 	1	**3c** 	98
4	**1d** 	1	**3d** 	98
5	**1e** 	10	**3e** 	93
6	**1f** 	30	**3f** 	94
7	**1g** 	10	**3g** 	92

[a] R: 

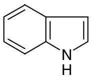
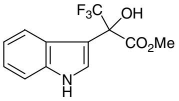
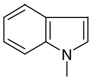
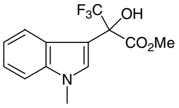
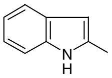
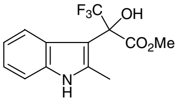
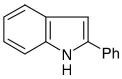
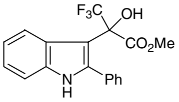
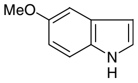
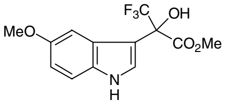
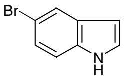
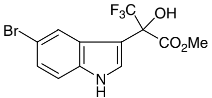
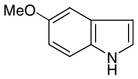
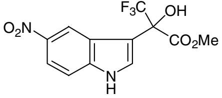
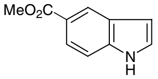
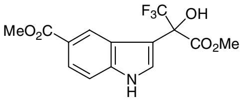
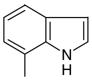
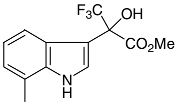
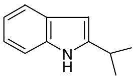
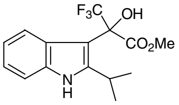
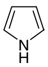
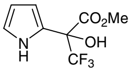
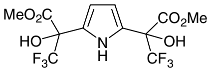
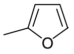
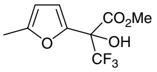
[b] Isolated yield.

was observed as demonstrated by short reaction time (1–10 min), except the case of **1f** (entry 6, 30 min), and excellent yields of alkylation products (**3a**–**g**, 92→99%). The *para*-substituted products of C-nucleophilic addition were isolated as a single regioisomer, which demonstrated that this solvent- and catalyst-free Friedel–Crafts alkylation had excellent *para*-regioselectivity. For *N*-methylanilines (**1b** and **1d**) and *N*-methyl-α-aminonaphthalene (**1g**) with an N–H group, the product of N-nucleophilic addition was not detected in the reaction mixture.

Subsequently, we focused on the solvent- and catalyst-free Friedel–Crafts alkylation of heteroaromatic compounds with **2** (Scheme 1). Surya Prakash and co-workers[4b] reported that the reaction of indole (**4a**) with **2** could be realized in ether solution without using a catalyst, as long as an extremely long reaction time was given (90 h, Table 1, entry 8). It was showed in Table 1 that in toluene and dichloromethane solutions without a catalyst, the reaction also proceeded very slowly (entries 9–10). However, under solvent- and catalyst-free condition, the reaction of **4a** with **2** occurred and was finished at room temperature ultra rapidly (within just 1 min like a 'flash' moment, Table 1, entry 11). Various indole derivatives (**4a**–**j**) were used for the solvent- and catalyst-free Friedel–Crafts alkylation reactions with **2** (Scheme 1). All the reactions needed only 1 min to be completed. The structures of the products (**5a**–**j**) and the corresponding yields were summarized in Table 3. The reactions gave excellent yields (76–98%) except **5d** and **5j**, which were probably due to the steric effect of the substituent at the 2-position of the indole ring. The yield of **5j** can be increased to 83% by prolonging reaction time to 2 h (entry 11). The presence of an electron-withdrawing group at the 5-position of the indole ring led to slightly lower yields of the compounds (**5g** and **5h**). Although the bisindolyl compounds were always generated in catalytic Friedel–Crafts alkylation of indoles with carbonyl compounds because of the intrinsic instability of the initial formed monoindolyl product, under homogeneous, heterogeneous[13] and solvent-free catalysis,[14] the formation of bisindolyl compound could be avoided by employing the solvent- and catalyst-free reaction conditions to give monoindolyl compounds exclusively.

Under the same reaction conditions (room temperature, reaction time: 1 min), pyrrole (**6**) and 2-methylfurane (**7**) underwent solvent- and catalyst-free Friedel–Crafts alkylation with **2** to give aminoalkylation products **9a** and **10** in yields of >99% and 95% (entries 12 and 14),

Table 3. The Friedel–Crafts reaction product of heteroaromatics with **2**[a]

Entry	Indole		Product		Yield[b] (%)
1	**4a**		**5a**		98
2	**4b**		**5b**		97
3	**4c**		**5c**		94
4	**4d**		**5d**		69
5	**4e**		**5e**		98
6	**4f**		**5f**		94
7	**4g**		**5g**		89
8	**4h**		**5h**		76
9	**4i**		**5i**		96
10	**4j**		**5j**		57
11	**4j**		**5j**		83[c]
12	**6**		**9a**		>99
13	**6**[d]		**9b**		96
14	**7**		**10**		95

[a] Reaction at room temperature for 1 min.

[b] Isolated yield.

[c] Reaction time: 2 h.

[d] **6**/**2** = 1:2.

respectively. However, if the ratio of **6** to **2** was changed to 1:2, the bis-alkylated pyrrole **9b** was obtained exclusively in a yield of 96% (entry 13).

In conclusion, a solvent- and catalyst-free Friedel–Crafts alkylation of aromatic and heteroaromatic compounds with methyl trifluoropyruvate proceeded rapidly in good to excellent yields. In most cases, the synthetic approaches exhibited high efficiency. Although the acceleration effect in solvent-free organic reaction has usually been attributed to concentration effect, the exact reasons for remarkable acceleration in the solvent- and catalyst-free Friedel–Crafts reaction definitely requires in depth investigation.

Acknowledgements

We thank the financial support for this research work by National Natural Science Foundation of China and Chinese Academy of Sciences.

References and notes

1. (a) Olah, G. A.; Khrisnamurti, R.; Surya Prakashi, G. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, pp 293–339; For review on stereoselective Friedel–Crafts alkylation reaction, see: (b) Bandini, M.; Melloni, A.; Umani-Rouchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.
2. (a) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552; (b) Lei, F.; Chen, Y.-J.; Sui, Y.; Liu, L.; Wang, D. *Synlett* **2003**, 1160; (c) Chen, Y. J.; Lei, F.; Liu, L.; Wang, D. *Tetrahedron* **2003**, *59*, 7609.
3. (a) Ishii, A.; Soloshonok, V. A.; Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597; (b) Chen, Y.-J.; Ge, C.-S.; Wang, D. *Synlett* **2000**, 1429; (c) Jørgensen, K. A. *Synthesis* **2003**, 1117; (d) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858.
4. (a) Dessole, G.; Herrera, R. P.; Ricci, A. *Synlett* **2004**, 2374; (b) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Surya Prakash, G. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086.
5. For a review on recent advances in solventless organic reactions, see: Cave, G. W. V.; Raston, G. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159.
6. Anastas, P. T.; Warner, J. C. *Green Chemistry—Theory and Practice*; Oxford University Press: New York, 1998.
7. (a) Nelson, D. W.; Owens, J.; Hiraldo, D. *J. Org. Chem.* **2001**, *66*, 2572; (b) Surya Prakash, G. K.; Manadal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589; (c) Bravo, P.; Crucianelli, M.; Vergani, B.; Zanda, M. *Tetrahedron Lett.* **1998**, *39*, 7771; (d) Xu, Y.; Dolbier, W. R., Jr. *Tetrahedron Lett.* **1998**, *39*, 9151.
8. (a) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009; (b) Corma, A.; Garcia, H.; Moussaif, A.; Sabater, M. J.; Zniber, R.; Redouuane, A. *Chem. Commun.* **2002**, 1058.
9. Surya Prakash, G. K.; Yan, P.; Torok, B.; Olah, G. A. *Synlett* **2003**, 527.
10. Ding, R.; Zhang, H. B.; Chen, Y. J.; Liu, L.; Wang, D.; Li, C.-J. *Synlett* **2004**, 555.
11. A typical experimental procedure was as follow: To indole (**4a**, 0.3 mmol) in a test tube was added dropwise methyl trifluoropyruvate (**2**, 0.3 mmol) at ambient temperature. The reaction was stirred for 1 min. The crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:4) to give a light red solid **5a**[12] (96%). According to the procedure, various compounds were synthesized, which were characterized by ^{1}H and ^{13}C NMR, IR and HRMS or elemental analysis.
12. Kato, K.; Fujii, S.; Gong, Y.-F.; Tanaka, S.; Katayama, M.; Kimoto, H. *J. Fluorine Chem.* **1999**, *99*, 5.
13. (a) Yadav, J. S.; Subba Reddy, B. V.; Murthy, Ch. V. S. R.; Mahesh Kumar, G.; Madan, Ch. *Synthesis* **2001**, 783; (b) Hao, J.; Taktak, S.; Aikawa, K.; Yusa, Y.; Hatano, M.; Mikami, K. *Synlett* **2001**, 1443; (c) Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. *Adv. Synth. Catal.* **2003**, *345*, 557.
14. Bartoli, G.; Bosco, M.; Foglia, G.; Giulani, A.; Marcantoni, E.; Sambri, L. *Synthesis* **2004**, 895.