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Formal [2+2+1] Synthesis of Tetrasubstituted Furans from Aldehydes, Acetylenedicarboxylates and Acyl Compounds

Keiichiro Tateishi,[a] Yuri Matsumoto,[a] and Akio Saito*[a]

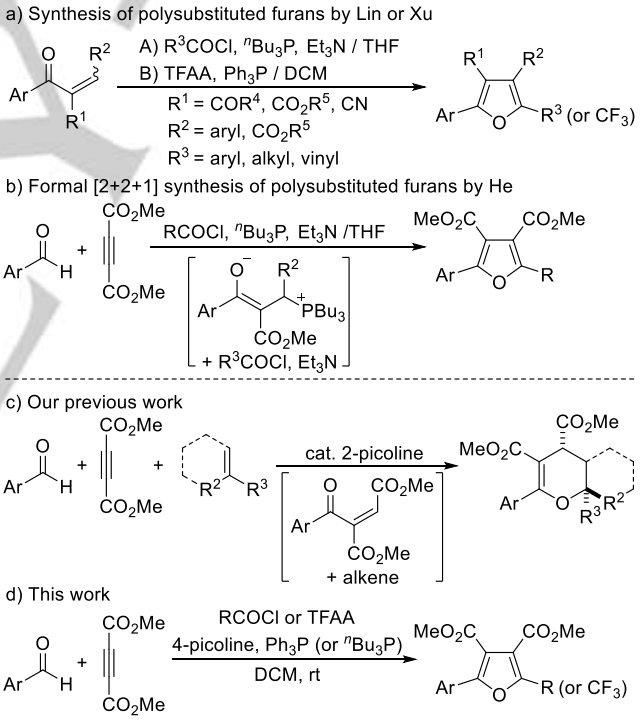
Dedication ((optional))

Abstract: A combination of 4-picoline and Ph_3P (or $^nBu_3P$) efficiently promotes a formal [2+2+1] synthesis of tetrasubstituted furans from aldehydes, acetylenedicarboxylates and acyl compounds under the metal-free and mild conditions. The present method can be applied not only to acyl chlorides but also trifluoroacetic anhydride as the acyl compounds. These furan products were formed in moderate to excellent yields via O-acylation of the α,β-enone intermediates followed by intramolecular Wittig reaction. From the results of control experiments, it was found that 4-picoline would serve as promoters in both formation of α,β-enones and O-acyl intermediates as well as a base for capture of acid.

Introduction

Highly functionalized furan rings are very important fundamental heterocyclic motifs found broad applications in medicinal, agrochemical, and material science.[1] Furans have also been frequently used as building blocks in synthetic chemistry.[2] Therefore, many synthetic routes toward furan rings with specific substitution patterns have been developed.[3] For the construction of tetrasubstituted furans, Paal-Knorr synthesis and its variants,[4] Feist-Bénary synthesis and its variants,[5] metal-catalyzed cyclization of highly substituted unsaturated ketones and alcohols,[6] formal [3+2] annulation of 1,3-dicarbonyl compounds with propargyl ester or alcohol[7] and oxidative annulation of 1,3-dicarbonyl compounds with alkenes or alkynes[8] have been well studied.[9] However, the preparation of the highly substituted precursors requires multiple steps. Although metal-mediated/catalyzed formal [2+2+1] annulations[10] and metal-free methods using isocyanides[11] have been known as facile assembly tools of tetrasubstituted furans from relatively simple building blocks, these procedures are met with complicated operations and/or substrate limitations. Thus, the development of efficient synthetic methods of the tetrasubstituted furans with flexible substituent patterns still has been a challenging goal.

Lin *et al.* recently reported an elegant domino formation of polysubstituted furans from α,β-enones and acyl chlorides in single operation,[12] which proceed via $^nBu_3P$-mediated O-acylation/intramolecular Wittig reaction sequence under mild conditions (Scheme 1a, method A).[13] This strategy was extended to the synthesis of 2-trifluoromethylfurans, which are useful as basic structures of pharmacologically active compounds,[1c-f] from enones and trifluoroacetic anhydride (TFAA, method B) by Xu *et al*.[14] Very recently, He *et al*. developed a three-component approach for the furan synthesis via direct generation of phosphonium enolate zwitterions,[15] which are similar intermediates to those of Lin's method,[12] from dialkyl acetylenedicarboxylates and aldehydes with $^nBu_3P$ (Scheme 1b).[16] Unfortunately, there is still room for improvement of the product yields in He's method, which was not applied to carboxylic anhydrides instead of acyl chlorides.



Scheme 1. Synthetic methods of polysubstituted furans.

As part of our continuing studies on the metal-free and domino synthesis of heterocycles via the formation of α,β-enones from alkynes and carbonyl compounds,[17] we disclosed the formal [2+2+2] synthesis of pyrans based on the hetero-Diels-Alder reactions of alkenes with enones formed from aldehydes and acetylenedicarboxylates[18] by 2-picoline catalyst (Scheme 1c).[17e] As a further extension of our methods, we herein describe formal [2+2+1] synthesis of tetrasubstituted furans from aldehydes, acetylenedicarboxylates and acyl compounds using 4-picoline and Ph_3P (or $^nBu_3P$). Although it is concerned that

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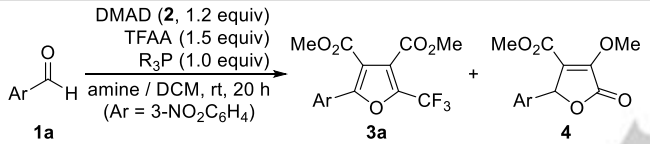
triaryl phosphine promotes the production of γ-butenolides from acetylenedicarboxylates with aldehydes or carboxylic anhydrides,[19] the present method can be applied not only to acyl chlorides but also carboxylic anhydrides such as TFAA (Scheme 1d). Furthermore, it was found from the results of control experiments that enone intermediates would be involved in these reactions.

Results and Discussion

Based on our reports on the formal [2+2+2] annulations[17e] and Xu's synthesis of 2-trifluoromethylfurans[14] (Scheme 1a, c), we attempted the formation of 2-trifluoromethylfurans **3a** from aldehyde **1a**, dimethyl acetylenedicarboxylate (DMAD, **2**, 1.2 equiv) and trifluoroacetic anhydride (TFAA, 1.5 equiv) in the presence of various amine and phosphines (1.0 equiv) in dichloromethane (DCM) at room temperature (Table 1).

Table 1. Optimization of the reaction conditions.



1a **3a** **4**

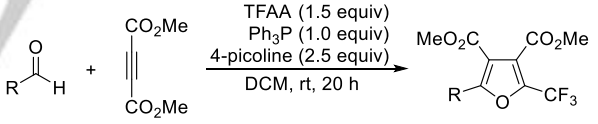
Entry	R_3P	Amine (equiv.)	**3a** [%]	**4** [%]
1	Ph_3P	None	54	44
2	Ph_3P	Pyridine (1.0)	65	31
3	Ph_3P	Pyridine (2.0)	73	23
4	$^nBu_3P$	Pyridine (2.0)	63	22
5	$(PhO)_3P$	Pyridine (2.0)	25[a]	0[b]
6	Ph_3P	DABCO (2.0)	54[a]	0
7	Ph_3P	DBU (2.0)	36[a]	0
8	Ph_3P	Et_3N (2.0)	38[a]	9[a]
9	Ph_3P	DMAP (2.0)	24[a]	ND[c]
10	Ph_3P	2,4,6-collidine (2.0)	50[a]	16[a]
11	Ph_3P	2,6-lutidine (2.0)	68[a]	14[a]
12	Ph_3P	4-picoline (2.0)	81	9
13	Ph_3P	4-picoline (2.5)	84	0
14	Ph_3P	4-picoline (3.0)	76	0
15[d]	$^nBu_3P$	Et_3N (1.2)	84	4

[a] Yields were determined by ^1H NMR analysis. [b] Recovery of **1a**: 32%. [c] Not determined. [d] $^nBu_3P$: 1.5 equiv, solvent: THF.

To our surprise, although the use of Ph_3P in the absence of amine afforded γ-butenolide **4** (44%) from **1a** and **2** as expected,[19] the desired furans **3a** was obtained in 54% yield as a main product (entry 1). Furthermore, the addition of pyridine (1 or 2 equiv, entry 2 or 3) improved the yields of **3a** up to 73% (entry 3). On the other hands, when $^nBu_3P$ or $(PhO)_3P$ was employed instead of Ph_3P (entry 4 or 5) and when relatively strong bases (pK_a = 18.2–24.1)[20] such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Et_3N and *N*,*N*-dimethyl-4-aminopyridine (DMAP) were added instead of pyridine (pK_a = 12.5,[20] entries 6–9), the yields of **3a** were reduced due to slower reaction (recovery of **1a**: 32%, entry 5) or complicated mixtures (entries 4, 6–9). However, pyridines such as 2,4,6-collidine, 2,6-lutidine and 4-picoline (pK_a = 14.1–15.0)[20] in the presence of Ph_3P gave relatively good results (entries 10–12). In particular, 4-picoline (2.5 equiv) improved the yields of **3a** up to 84% without the detection of **4** (entry 13). It should be mentioned that the combination of $^nBu_3P$ and Et_3N in THF reported by Lin[12] and He[16] did not show better results (entry 15).

Under the optimized reaction conditions, the scope for the synthesis of 2-trifluoromethylfurans **3** from various aldehydes **1**, DMAD (**2**, 1.2 equiv) and TFAA (1.5 equiv) is summarized in Table 2. Similar to 3-nitrobenzaldehyde (**1a**, entry 1), aromatic aldehyde **1b–f** bearing electron-withdrawing groups were smoothly converted to the corresponding furans **3b–f** within 24 h in 73–83% yields (entries 2–6). On the other hand, in cases of benzaldehyde (**1g**) and furfural (**1h**), the use of $^nBu_3P$ instead of Ph_3P gave better results (**3g**: 42%, **3h**: 53%, entries 7 and 8).

Table 2. Scope for the synthesis of 2-CF_3-substituted furans **3**.



1 **2** (1.2 equiv) **3**

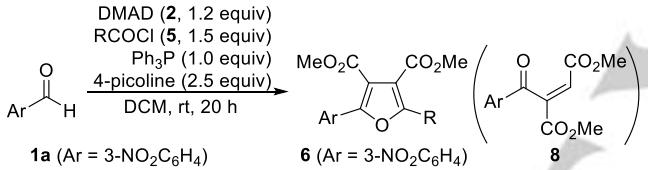
Entry	**1**	R	**3**	Yield [%]
1	**1a**	3-$NO_2C_6H_4$	**3a**	84
2	**1b**	2-$NO_2C_6H_4$	**3b**	76
3	**1c**	4-$NO_2C_6H_4$	**3c**	83
4	**1d**	4-CNC_6H_4	**3d**	81
5	**1e**	4-$CF_3C_6H_4$	**3e**	73
6	**1f**	4-BrC_6H_4	**3f**	76
7	**1g**	Ph	**3g**	34 (42)[a]
8	**1h**	2-furyl	**3h**	39 (53)[a]

[a] Values in parentheses were yields using $^nBu_3P$ instead of Ph_3P.

Notably, the present methods could not be applied to aliphatic aldehydes such as ^{t}BuCHO, ^{i}PrCHO and EtCHO. It was known that the base-catalyzed formation of a,b-enones from aliphatic aldehydes and DMAD (**2**) did not proceed efficiently.[18]

Subsequently, we examined a formal [2+2+1] synthesis of other substituted furans using various acyl chlorides **5** or other carboxylic anhydrides (Table 3). To our delight, regardless of aromatic and aliphatic acyl chlorides (1.5 equiv), the combination of Ph_3P and 4-picoline promoted the reaction of aldehyde **1a** and DMAD (**2**, 1.2 equiv) to give the corresponding furans **6a–j** in high yields (74%–quant) at room temperature (entries 1-10). Also, by using $^{n}Bu_3P$ instead of Ph_3P, furans **7c** and **7g** were obtained from benzaldehyde (**1g**), DMAD (**2**) and acyl chlorides **5c** or **5g** in better yields (**7c**: 56%, **7g**: 50%, entries 11 and 12). Unfortunately, even when 3 equiv of acetic anhydride (Ac_2O) was employed instead of acetyl chloride (**5a**), the yield of **6a** was reduced up to 58% along with the formation of α,β-enone **8** in 26% yield (entry 1). Assuming that α,β-enone **8** is formed from **1a** and **2**[17e,18,19b,c] as an intermediate converted to furans **6**, this result suggest that the part of intermediate **8** would be recovered due to lower acylation ability of Ac_2O.

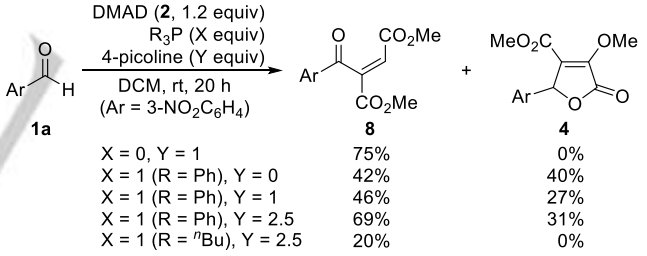
Table 3. Scope for the synthesis of furans **6**.



Entry	**5**	R	**6** or **7**	Yield [%]
1	**5a**	Me	**6a**	74 (58)[a]
2	**5b**	^{i}Pr	**6b**	86
3	**5c**	^{t}Bu	**6c**	quant
4	**5d**	Ph	**6d**	92
5	**5e**	2-ClC_6H_4	**6e**	82
6	**5f**	3-ClC_6H_4	**6f**	87
7	**5g**	4-ClC_6H_4	**6g**	89
8	**5i**	4-$NO_2C_6H_4$	**6h**	89
9	**5j**	4-MeC_6H_4	**6i**	82
10	**5k**	4-$MeOC_6H_4$	**6j**	81
11	**5c**	^{t}Bu	**7c**	31 (56)[b]
12	**5g**	4-ClC_6H_4	**7g**	32 (50)[b]

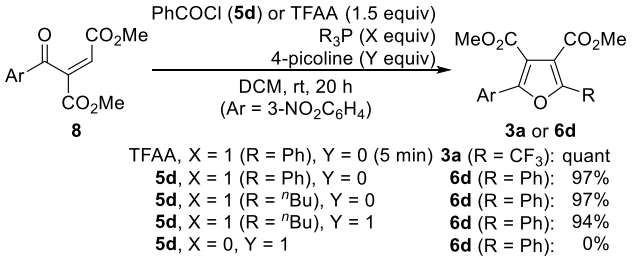
[a] Value in parenthesis was yield using Ac_2O (3 equiv) instead of **5a**. In this case, α,β-enone **7** was formed in 26% yield. [b] Values in parentheses were yields using $^{n}Bu_3P$ instead of Ph_3P.

In order to gain an insight into the involvement of α,β-enone **8** as the intermediate, we carried out the formation of **8** from aldehyde **1a** with DMAD (**2**) as control experiments (Scheme 2). By solely using 4-picoline (1 equiv) in DCM at room temperature, enone **8** was obtained in good yield (75%). On the other hand, regardless of the presence or absence of 4-picoline, Ph_3P (1 equiv) afforded γ-butenolide **4** (40% or 27%) along with enone **8** (42% or 46%). However, when the amount of 4-picoline was increased up to 2.5 equiv, the yield of **8** was increased up to 69% albeit γ-butenolide **4** was formed (31%). Considering that γ-butenolides were not detected in the present synthesis of furans **3**, **6** and **7** using Ph_3P and 4-picoline, the formation process of α,β-enone would be involved as a main route to the furans. Notably, the both conversion of **8** into **4** by Ph_3P and of **4** into **8** by 4-picoline were not actually observed. Therefore, 4-picoline would play the role as a major promoter in the formation of **8** under the optimal conditions, although the involvement of Ph_3P cannot be ignored. On the other hand, the use of $^{n}Bu_3P$ instead of Ph_3P even in the presence of 4-picoline (2.5 equiv) gave enone **8** in only 20%, albeit no formation of γ-butenolide **4** (Scheme 2). This result suggests that α,β-enone intermediates would partially be involved in the 4-picoline/$^{n}Bu_3P$-mediated reactions. It is known that the phosphonium enolate zwitterions (like intermediates shown in Scheme 1b), derived from alkynoates and aldehydes with trialkylphosphines, are relatively stable.[15]



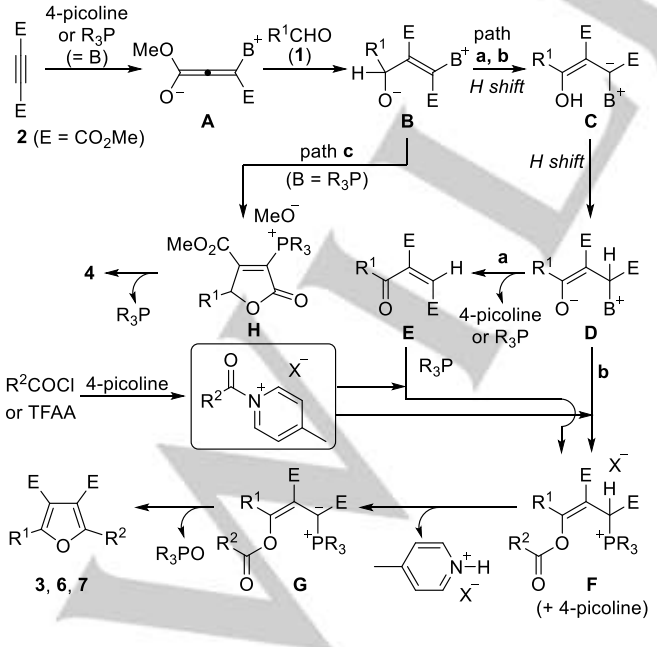
Scheme 2. Formations of **8** from **1a** and **2**.

Next, the conversions of **3a** or **6d** from α,β-enone **8** with TFAA or PhCOCl were checked as part of control experiments (Scheme 3). Similar to Xu's synthesis of 2-trifluoromethylfurans,[14] in the absence of 4-picoline, Ph_3P led to the formation of furan **3a** from **8** and TFAA in quantitative yield at room temperature within 5 min. Interestingly, the sole use of Ph_3P or $^{n}Bu_3P$ also promoted the reaction of **8** with benzoyl chloride (**5d**) to give furans **6d** in high yields (97% in both cases), although amines were required for the deprotonation of O-acyl intermediates to phosphonium ylides in the Lin's furan synthesis using $^{n}Bu_3P$.[12] Therefore, the deprotonation to phosphonium ylides would be occurred by chloride anions and thus amines would essentially work as scavengers of the generated HCl in the present methods.



Scheme 3. Formations of **3a** or **6d** from **8** with TFAA or **5d**.

On the basis of these results and previous reports of phosphines-mediated syntheses of furans,[12–16] a mechanism for the formal [2+2+1] synthesis of furans **3**, **6** and **7** was proposed (Scheme 4). Initially, DMAD (**2**) undergo a Michael-type addition with 4-picoline or R_3P (R = Ph or ^{n}Bu) to from enolates **A**, which react with aldehydes **1** giving rise to intermediates **B**. Next, a C-to-O 1,2-H-shift of the intermediates **B** followed by a O-to-C 1,4-H-shift of the intermediates **C** afford α,β-enones **E** after an elimination of 4-picoline or R_3P in intermediates **D** (path **a**). Since 4-picoline is mainly involved in a series of these processes, γ-butenolide **4** would be not formed from the intermediates **B** (path **c**).[19a–c] Subsequently, the α,β-enones **E** are converted to intermediates **F** via the regeneration of the intermediates **D** by R_3P and an O-acylation of **D** with acyl compounds. Part of the phosphonium intermediates **D** (B = R_3P) directly undergo the O-acylation with acyl compounds (path **b**). Possibly, 4-picoline promotes the O-acylation of **D** via the generation of *N*-acyl pyridinium intermediates.[21] Finally, after deprotonation of the intermediates **F** along with capture of acid (X = CF_3COO or Cl) by 4-picoline, an intramolecular Wittig reaction of the resulting ylides **F** occurs furans.



Scheme 4. Proposed mechanism.

Conclusions

We have developed a formal [2+2+1] synthesis of tetrasubstituted furans from aldehydes, alkynoates and TFAA or acyl chlorides using 4-picoline and Ph_3P (or $^nBu_3P$) under metal-free and mild conditions. Furthermore, from the results of control experiments, we proposed that α,β-enones would be involved as intermediates and 4-picoline would play not only the role of base for capture of acid but also that of promoter in both formation of α,β-enones and O-acyl intermediates. Although the similar [2+2+1] method has been reported by He *et al.*, our findings provide an alternative procedure for the access to the polysubstituted furans including 2-trifluoromethylfurans in relatively good yields.

Experimental Section

General information. 4-Picoline, triphenylphosphine tri-*n*-butylphosphine, aldehydes **1a–h**, dimethyl acetylenedicarboxylate (**2**), trifluoroacetic anhydride (TFAA), and acyl chlorides **5a–j** are commercially available. Products **4**[19b] and **8**[18b] are known compounds. Dichloromethane (DCM) was purchased as the "anhydrous" and used without further purification. ^{1}H and ^{13}C NMR spectra were measured at 500 (or 300) and 125 (or 75) MHz in $CDCl_3$, and the chemical shifts are given in ppm using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for 1H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as an internal standard, respectively. Splitting patterns of an apparent multiplet associated with an averaged coupling constant were designed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broadened). Mass spectra (HRMS) were recorded by FAB methods. All reactions were carried out under an argon atmosphere.

General procedure for synthesis of furans 3, 6 and 7: To a solution of aldehyde **1a-h** (0.4 mmol) and dimethyl acetylenedicarboxylate (**2**, 59.0 µL, 0.48 mmol) in DCM (2.0 ml) was added 4-picoline (95.5µL, 1.0 mmol), triphenylphosphine (for **1a-1f**, 105 mg, 0.4 mmol) or tributylphosphine (for **1g** and **1h**, 98.7 µL, 0.4 mmol) and TFAA (83.5 µL, 0.6 mmol) or acyl chloride **5** (0.6 mmol) at room temperature. After being stirred at same temperature for 20 h, the reaction mixture was quenched with sat. $NaHCO_3$ and then extracted with AcOEt. The organic layer was dried over MgSO4 and concentrated in vacuo to dryness. The residue was purified by medium-pressure liquid chromatography (MPLC, hexane:AcOEt = 95:5 to 50:50, flow rate 20 mL/min) to give **3**, **6** or **7**.

Dimethyl 2-(3-nitrophenyl)-5-(trifluoromethyl)furan-3,4-dicarboxylate (3a): MPLC: 24 min (hexane:AcOEt = 80:20). 125.4 mg (84%). White solid. ^{1}H NMR (500 MHz) δ ppm; 8.77 (s, 1H; Ar-H), 8.32 (d, *J* = 8.0 Hz, 1H; Ar-H), 8.22 (d, *J* = 8.0 Hz, 1H; Ar-H), 7.68 (t, *J* = 8.0 Hz, 1H; Ar-H), 3.94 (s, 3H; CH_3), 3.89 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 162.1 (C=O), 161.5 (C=O), 154.6 (C), 148.6 (C), 140.4 (q, $J_{C,F}$ = 44.0 Hz; *C*-CF_3), 134.1 (CH), 130.0 (CH), 129.1 (C), 125.5 (CH), 123.5 (CH), 122.0 (q, $J_{C,F}$ = 2.4 Hz, C), 118.2 (q, $J_{C,F}$ = 269.5 Hz; CF_3), 115.8 (C), 53.0 (CH_3), 52.8 (CH_3). The ^{1}H and ^{13}C NMR spectra of **3a** were identical to data reported in the literature.[14]

Dimethyl 2-(2-nitrophenyl)-5-(trifluoromethyl)furan-3,4-dicarboxylate (3b): MPLC: 22 min (hexane:AcOEt = 67:33). 113.5 mg (76%). Colorless oil. IR (neat) ν cm^{-1}; 1741, 1622, 1533, 1443, 1351, 1237, 1156. ^{1}H NMR (500 MHz) δ ppm; 8.18 (dd, *J* = 8.0, 1.2 Hz, 1H; Ar-H), 7.79-7.69 (m, 2H; Ar-H), 7.63 (dd, *J* = 7.5, 1.7 Hz, 2H; Ar-H), 3.94 (s, 3H; CH_3), 3.69 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 161.8 (C=O), 161.2 (C=O), 155.1 (C),

148.7 (C), 140.0 (q, $J_{C,F}$ = 43.5 Hz; *C*-CF_3), 133.5 (CH), 132.9 (CH), 132.2 (CH), 125.2 (CH), 123.0 (C), 121.4 (C), 118.2 (q, $J_{C,F}$ = 268.7 Hz; CF_3), 115.5 (C), 53.1 (CH_3), 52.2 (CH_3). HRMS (FAB) m/z: Calcd for $C_{15}H_{11}F_3NO_7$ $[M+H]^+$ 374.0488; Found: 374.0517.

Dimethyl 2-(4-nitrophenyl)-5-(trifluoromethyl)furan-3,4-dicarboxylate (3c): MPLC: 21 min (hexane:AcOEt = 80:20). 123.9 mg (83%). Pale yellow solid. MP 86-87 ºC. IR (neat) ν cm^{-1}; 1737, 1624, 1526, 1442, 1345, 1255, 1173. ^{1}H NMR (500 MHz) δ ppm; 8.31 (d, *J* = 8.8 Hz, 2H; Ar-H), 8.06 (d, *J* = 8.8 Hz, 2H; Ar-H), 3.94 (s, 3H; CH_3), 3.89 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 162.3 (C=O), 161.3 (C=O), 154.2 (C), 149.0 (C), 141.0 (q, $J_{C,F}$ = 43.6 Hz; *C*-CF_3), 133.2 (C), 129.2 (CH), 124.1 (CH), 121.9 (q, $J_{C,F}$ = 2.4 Hz; C), 118.2 (q, $J_{C,F}$ = 269.9 Hz; CF_3), 116.6 (C), 53.1 (CH_3), 52.8 (CH_3). HRMS (FAB) m/z: Calcd for $C_{15}H_{11}F_3NO_7$ $[M+H]^+$ 374.0488; Found: 374.0511.

Dimethyl 2-(4-cyanophenyl)-5-(trifluoromethyl)furan-3,4-dicarboxylate (3d): MPLC: 28 min (hexane:AcOEt = 80:20). 114.5 mg (81%). White solid. ^{1}H NMR (500 MHz) δ ppm; 7.98 (d, *J* = 8.6 Hz, 2H; Ar-H), 7.75 (d, *J* = 8.6 Hz, 2H; Ar-H) 3.93 (s, 3H; CH_3), 3.87 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 162.3 (C=O), 161.3 (C=O), 154.5 (C), 140.7 (q, $J_{C,F}$ = 44.0 Hz; *C*-CF_3), 133.6 (CH), 131.5 (C), 128.7 (CH), 121.8 (q, $J_{C,F}$ = 2.4 Hz; C), 118.2 (CN), 118.1 (q, $J_{C,F}$ = 269.9 Hz; CF_3), 116.2 (C), 114.3 (C), 53.0 (CH_3), 52.7 (CH_3). The ^{1}H and ^{13}C NMR spectra of **3d** were identical to data reported in the literature.[14]

Dimethyl 2-(trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)furan-3,4-dicarboxylate (3e): MPLC: 19 min (hexane:AcOEt = 90:10). 115.7 mg (73%). Colorless oil. ^{1}H NMR (500 MHz) δ ppm; 7.98 (d, *J* = 8.3 Hz, 2H; Ar-H), 7.72 (d, *J* = 8.3 Hz, 2H; Ar-H) 3.94 (s, 3H; CH_3), 3.87 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 162.5 (C=O), 161.6 (C=O), 155.4 (C), 140.5 (q, $J_{C,F}$ = 43.6 Hz; *C*-CF_3), 132.7 (q, $J_{C,F}$ = 32.8 Hz; *C*-CF_3), 130.9 (C), 128.8 (CH), 125.9 (q, *J* = 3.6 Hz; CH), 123.9 (q, $J_{C,F}$ = 272.3 Hz; CF_3), 121.8 (q, $J_{C,F}$ = 2.4 Hz; C), 118.2 (q, $J_{C,F}$ = 269.5 Hz; CF_3), 115.6 (C), 53.0 (CH_3), 52.6 (CH_3). The ^{1}H and ^{13}C NMR spectra of **3e** were identical to data reported in the literature.[14]

Dimethyl 2-(4-bromophenyl)-5-(trifluoromethyl)furan-3,4-dicarboxylate (3f): MPLC: 27 min (hexane:AcOEt = 95:5). 115.7 mg (76%). 123.8 mg (73%). White solid. ^{1}H NMR (500 MHz) δ ppm; 7.73 (d, *J* = 8.9 Hz, 2H; Ar-H), 7.60 (d, *J* = 8.9 Hz, 2H; Ar-H) 3.93 (s, 3H; CH_3), 3.85 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 162.6 (C=O), 161.8 (C=O), 156.4 (C), 139.8 (q, $J_{C,F}$ = 43.6 Hz; *C*-CF_3), 132.2 (C), 129.9 (CH), 126.5 (C), 125.8 (C), 121.8 (q, $J_{C,F}$ = 2.4 Hz; C), 118.4 (q, $J_{C,F}$ = 269.5 Hz; CF_3), 114.5 (C), 52.9 (CH_3), 52.5 (CH_3). The ^{1}H and ^{13}C NMR spectra of **3f** were identical to data reported in the literature.[14]

Dimethyl 2-phenyl-5-(trifluoromethyl)furan-3,4-dicarboxylate (3g): MPLC: 32 min (hexane:AcOEt = 95:5). 55.5 mg (42%). Colorless oil. ^{1}H NMR (500 MHz) δ ppm; 7.86-7.81 (m, 2H; Ar-H), 7.51-7.44 (m, 3H; Ar-H), 3.94 (s, 3H; CH_3), 3.86 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 162.9 (C=O), 161.9 (C=O), 157.4 (C), 139.7 (q, $J_{C,F}$ = 43.6 Hz; *C*-CF_3), 131.1 (CH), 128.9 (CH), 128.4 (CH), 127.7 (C), 121.6 (q, $J_{C,F}$ = 2.4 Hz; C), 118.5 (q, $J_{C,F}$ = 269.5 Hz; CF_3), 114.2 (C), 52.9 (CH_3), 52.5 (CH_3). The ^{1}H and ^{13}C NMR spectra of **3g** were identical to data reported in the literature.[14]

Dimethyl 5-(trifluoromethyl)-[2,2'-bifuran]-3,4-dicarboxylate (3h): MPLC: 26 min (hexane:AcOEt = 95:5). 63.9 mg (53%). White solid. ^{1}H NMR (300 MHz) δ ppm; 7.61 (d, *J* = 1.5 Hz, 1H; Ar-H), 7.49 (d, *J* = 3.7 Hz, 1H; Ar-H), 6.57 (dd, *J* = 3.7, 1.5 Hz, 1H; Ar-H), 3.93 (s, 3H; CH_3), 3.88 (s, 3H; CH_3). ^{13}C NMR (75 MHz) δ ppm; 161.6 (C=O), 161.4 (C=O), 149.1 (C), 145.2 (CH), 142.3 (C), 138.2 (q, $J_{C,F}$ = 43.5 Hz; *C*-CF_3), 121.5 (q, $J_{C,F}$ = 2.0 Hz; C), 118.2 (q, $J_{C,F}$ = 269.0 Hz; CF_3), 115.8 (CH), 112.3 (CH), 111.6 (C), 53.1 (CH_3), 52.4 (CH_3). The ^{1}H and ^{13}C NMR spectra of **3g** were identical to data reported in the literature.[14]

Dimethyl 2-methyl-5-(3-nitrophenyl)furan-3,4-dicarboxylate (6a): MPLC: 32 min (hexane:AcOEt = 95:5). 94.9 mg (74%). Pale yellow solid. MP 111-112 ºC. IR (KBr) ν cm^{-1}; 1736, 1719, 1528, 1449, 1348, 1245. ^{1}H NMR (500 MHz) δ ppm; 8.54 (t, *J* = 2.0 Hz, 1H; Ar-H), 8.19-8.15 (m, 1H; Ar-H), 8.02-7.99 (m, 1H; Ar-H), 7.57 (t, *J* = 8.3 Hz, 1H; Ar-H), 3.93 (s, 3H; CH_3) , 3.85 (s, 3H; CH_3), 2.63 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 165.3 (C=O), 163.4 (C=O), 159.3 (C), 148.8 (C), 148.3 (C), 131.7 (CH), 130.6 (C), 130.1 (CH), 123.5 (CH), 121.0 (CH), 116.5 (C), 115.0 (C), 52.7 (CH_3), 51.8 (CH_3), 13.3 (CH_3). HRMS (FAB) m/z: Calcd for $C_{15}H_{14}NO_7$ $[M+H]^+$ 320.0770; Found: 320.0741.

Dimethyl 2-isopropyl-5-(3-nitrophenyl)furan-3,4-dicarboxylate (6b): MPLC: 23 min (hexane:AcOEt = 80:20). 119.2 mg (86%). Pale yellow solid. MP 88-89 ºC. IR (KBr) ν cm^{-1}; 1729, 1710, 1530, 1441, 1351, 1228. ^{1}H NMR (300 MHz) δ ppm; 8.54 (br.s, 1H, Ar-H), 8.20 (br.d, *J* = 8.1 Hz, 1H; Ar-H), 8.02 (br.d, *J* = 8.1 Hz, 1H, Ar-H), 7.59 (t, *J* = 8.1 Hz, 1H; Ar-H), 3.93 (s, 3H; CH_3), 3.86 (s, 3H; CH_3), 3.70 (septet, *J* = 7.0 Hz, 1H; CH), 1.35 (d, *J* = 7.0 Hz, 6H; CH_3). ^{13}C NMR (75 MHz) δ ppm; 166.5 (C=O, 165.0 (C=O), 163.0 (C), 148.5 (C), 147.8 (C), 131.6 (CH), 130.5 (C), 129.9 (CH), 123.4 (CH), 120.9 (CH), 116.2 (C), 113.1 (C), 52.8 (CH_3), 52.0 (CH_3), 27.2 (CH), 20.6 (CH_3). HRMS (FAB) m/z: Calcd for $C_{17}H_{18}NO_7$ $[M+H]^+$ 348.1083; Found: 348.1080.

Dimethyl 2-(tert-butyl)-5-(3-nitrophenyl)furan-3,4-dicarboxylate (6c): MPLC: 18 min (hexane:AcOEt = 80:20). 148.1 mg (quant). Pale yellow solid. MP 84-85 ºC. IR (KBr) ν cm^{-1}; 1743, 1715, 1534, 1439, 1352, 1213. ^{1}H NMR (300 MHz) δ ppm; 8.71 (t, *J* = 1.8 Hz, 1H; Ar-H), 8.21 (dt, *J* = 8.1, 1.8 Hz, 1H; Ar-H), 8.17 (dt, *J* = 8.1, 1.8 Hz, 1H; Ar-H), 7.61 (t, *J* = 8.1 Hz, 1H; Ar-H), 3.88 (s, 3H; CH_3), 3.84 (s, 3H; CH_3), 1.40 (s, 9H; CH_3) ^{13}C NMR (75 MHz) δ ppm; 165.2 (C=O), 163.3 (C=O), 162.5 (C), 150.4 (C), 148.3 (C), 133.4 (CH), 130.7 (C), 129.4 (CH), 123.8 (CH), 122.7 (CH), 115.3 (C), 114.7 (C), 52.4 (CH_3), 52.3 (CH_3), 34.3 (C), 28.5 (CH_3). HRMS (FAB) m/z: Calcd for $C_{18}H_{20}NO_7$ $[M+H]^+$ 362.1240; Found: 362.1247.

Dimethyl 2-(3-nitrophenyl)-5-phenylfuran-3,4-dicarboxylate (6d): MPLC: 29 min (hexane:AcOEt = 80:20). 140.4 mg (92%). Yellow solid. MP 118-119 ºC. IR (KBr) ν cm^{-1}; 1739, 1725, 1531, 1437, 1351, 1238. ^{1}H NMR (500 MHz) δ ppm; 8.76 (t, *J* = 1.7 Hz, 1H; Ar-H), 8.26-8.20 (m, 2H; Ar-H), 7.87-7.81 (m, 2H; Ar-H), 7.62 (t, *J* = 8.1 Hz, 1H; Ar-H), 7.50-7.41 (m, 3H; Ar-H), 3.92 (s, 3H; CH_3), 3.89 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 164.3 (C=O), 163.9 (C=O), 154.5 (C), 151.1 (C), 148.7 (C), 131.2 (CH), 130.4 (C), 130.3 (CH), 129.9 (CH), 128.9 (CH), 128.4 (C), 127.5 (CH), 124.2 (CH), 122.4 (CH), 117.1 (C), 115.8 (C), 52.5 (CH_3), 52.4 (CH_3). HRMS (FAB) m/z: Calcd for $C_{20}H_{16}NO_7$ $[M+H]^+$ 382.0927; Found: 382.0920.

Dimethyl 2-(2-chlorophenyl)-5-(3-nitrophenyl)furan-3,4-dicarboxylate (6e): MPLC: 71 min (hexane:AcOEt = 90:10). 136.2 mg (82%). Pale yellow solid. MP 127-128 ºC. IR (KBr) ν cm^{-1}; 1725, 1531, 1434, 1355, 1255, 1080. ^{1}H NMR (300 MHz) δ ppm; 8.69 (br.s, 1H; Ar-H), 8.26 (br.d, *J* = 7.7 Hz, 1H; Ar-H), 8.17 (br.d, *J* = 8.4 Hz, 1H; Ar-H), 7.68-7.51 (m, 3H; Ar-H), 7.50-7.36 (m, 2H; Ar-H), 3.97 (s, 3H; CH_3), 3.77 (s, 3H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 163.9 (C=O), 162.4 (C=O), 152.9 (C), 150.6 (C), 148.4 (C), 134.0 (C), 132.4 (CH), 132.0 (CH), 131.48 (CH), 130.12 (C), 130.07 (CH), 129.8 (CH), 127.8 (C), 126.6 (CH), 123.9 (CH), 121.7 (CH), 118.0 (C), 116.4 (C), 52.9 (CH_3), 52.3 (CH_3). HRMS (FAB) m/z: Calcd for $C_{20}H_{15}ClNO_7$ $[M+H]^+$ 416.0537; Found: 416.0570.

Dimethyl 2-(3-chlorophenyl)-5-(3-nitrophenyl)furan-3,4-dicarboxylate (6f): MPLC: 62 min (hexane:AcOEt = 90:10). 144.1 mg (87%). Pale yellow solid. MP 137-138 ºC. IR (KBr) ν cm^{-1}; 1739, 1720, 1531, 1436, 1345, 1221, 1084. ^{1}H NMR (300 MHz) δ ppm; 8.76 (t, *J* = 1.8 Hz, 1H; Ar-H), 8.32-8.19 (m, 2H; Ar-H), 7.87-7.82 (m, 1H; Ar-H), 7.78-7.71 (m, 1H; Ar-H), 7.65 (t, *J* = 8.1 Hz, 1H; Ar-H), 7.45-7.38 (m, 2H; Ar-H), 3.92 (s, 3H; CH_3) , 3.91 (s, 3H; CH_3). ^{13}C NMR (75 MHz) δ ppm; 163.6 (C=O), 163.4 (C=O), 152.6 (C), 151.2 (C), 148.4 (C), 134.8 (C), 133.1 (CH), 130.1 (CH), 130.0 (C), 129.80 (C), 129.77 (CH), 127.3 (CH), 125.5 (CH), 124.2 (CH), 122.4 (CH), 117.1 (C), 116.5 (C), 52.71 (CH_3), 52.69 (CH_3) (note that two carbon peaks overlap with each other). HRMS (FAB) m/z: Calcd for $C_{20}H_{15}ClNO_7$ $[M+H]^+$ 416.0537; Found: 416.0544.

Dimethyl 2-(4-chlorophenyl)-5-(3-nitrophenyl)furan-3,4-dicarboxylate (6g): MPLC: 24 min (hexane:AcOEt = 80:20). 148.6 mg (89%). White solid. MP 129-130 ºC. IR (KBr) ν cm^{-1}; 1723, 1531, 1437, 1351, 1236, 1092. ^{1}H NMR (300 MHz) δ ppm; 8.75 (t, *J* = 1.6 Hz, 1H; Ar-H), 8.30-8.19 (m, 2H; Ar-H), 7.82 (d, *J* = 8.5 Hz, 2H; Ar-H), 7.65 (t, *J* = 8.0 Hz, 1H; Ar-H), 7.45 (d, *J* = 8.5 Hz, 2H; Ar-H), 3.93 (s, 3H; CH_3) , 3.90 (s, 3H; CH_3). ^{13}C NMR (75 MHz) δ ppm; 163.7 (C=O), 163.6 (C=O), 152.6 (C), 151.8 (C), 148.4 (C), 136.3 (C), 133.0 (CH), 130.4 (C), 130.1 (C), 129.8 (CH), 129.1 (CH), 128.8 (CH), 124.2 (CH), 122.3 (CH), 117.2 (C), 116.3 (C), 52.7 (CH_3), 52.6 (CH_3). HRMS (FAB) m/z: Calcd for $C_{20}H_{15}ClNO_7$ $[M+H]^+$ 416.0537; Found: 416.0545.

Dimethyl 2-(3-nitrophenyl)-5-(4-nitrophenyl)furan-3,4-dicarboxylate (6h): MPLC: 79 min (hexane:AcOEt = 80:20). 151.8 mg (89%). Yellow solid. MP 176-177 ºC. IR (KBr) ν cm^{-1}; 1739, 1720, 1528, 1438, 1348, 1234. ^{1}H NMR (300 MHz) δ ppm; 8.78 (br.s, 1H; Ar-H), 8.40-8.22 (m, 4H; Ar-H), 8.07 (d, *J* = 8.8 Hz, 2H; Ar-H), 7.69 (t, *J* = 8.1 Hz, 1H; Ar-H), 3.94 (s, 6H; CH_3). ^{13}C NMR (125 MHz) δ ppm; 161.1 (C=O), 160.9 (C=O), 158.5 (C), 154.2 (C), 148.1 (C), 147.8 (C), 133.2 (CH), 130.1 (C), 129.8 (CH), 129.7 (C), 127.9 (CH), 124.5 (CH), 124.0 (CH), 122.6 (CH), 118.3 (C), 117.4 (C), 53.0 (CH_3), 52.9 (CH_3). HRMS (FAB) m/z: Calcd for $C_{20}H_{15}N_2O_9$ $[M+H]^+$ 427.0778; Found: 427.0792.

Dimethyl 2-(3-nitrophenyl)-5-(4-tolyl)furan-3,4-dicarboxylate (6i): MPLC: 34 min (hexane:AcOEt = 85:15). 129.6 mg (82%). Yellow solid. MP 129-130 ºC. IR (KBr) ν cm^{-1}; 1730, 1525, 1444, 1348, 1229. ^{1}H NMR (500 MHz) δ ppm; 8.76 (t, *J* = 1.7 Hz, 1H; Ar-H), 8.26 (dt, *J* = 8.1, 1.7 Hz, 1H; Ar-H), 8.23 (dt, *J* = 8.1, 1.7 Hz, 1H; Ar-H), 7.75 (d, *J* = 8.0 Hz, 2H; Ar-H), 7.64 (t, *J* = 8.1 Hz, 1H; Ar-H), 7.29 (d, *J* = 8.0 Hz, 2H; Ar-H), 3.93 (s, 3H; CH_3), 3.89 (s, 3H; CH_3), 2.42 (s, 3H; CH_3). ^{13}C NMR (75 MHz) δ ppm; 164.0 (C=O), 163.8 (C=O), 154.8 (C), 150.4 (C), 148.4 (C), 140.5 (C), 132.9 (CH), 130.4 (C), 129.7 (CH), 129.4 (CH), 127.4 (CH), 125.5 (C), 123.9 (CH), 122.2 (CH), 117.0 (C), 115.0 (C), 52.6 (CH_3), 52.5 (CH_3), 21.4 (CH_3). HRMS (FAB) m/z: Calcd for $C_{21}H_{18}NO_7$ $[M+H]^+$ 396.1083; Found: 396.1097.

Dimethyl 2-(4-methoxyphenyl)-5-(3-nitrophenyl)furan-3,4-dicarboxylate (6j): MPLC: 14 min (hexane:AcOEt = 50:50). 132.2 mg (81%). Pale yellow solid. MP 101-102 ºC. IR (neat) ν cm^{-1}; 1727, 1525, 1444, 1348, 1258, 1229, 1053. ^{1}H NMR (300 MHz) δ ppm; 8.74 (br.s, 1H; Ar-H), 8.28-8.18 (m, 2H; Ar-H), 7.85 (d, *J* = 8.1 Hz, 2H; Ar-H), 7.63 (t, *J* = 8.1 Hz, 1H; Ar-H), 7.00 (d, *J* = 8.1 Hz, 2H; Ar-H), 3.93 (s, 3H; CH_3), 3.88 (s, 3H; CH_3), 3.88 (s, 3H; CH_3). ^{13}C NMR (75 MHz) δ ppm; 164.0 (C=O), 162.3 (C=O), 161.2 (C), 155.8 (C), 149.8 (C), 148.5(C), 132.7 (CH), 130.4 (C), 129.7 (CH), 129.4 (CH), 123.8 (CH), 122.0 (CH), 120.9 (C), 117.2 (CH), 114.1 (CH), 114.0 (C), 55.4 (CH_3), 52.7 (CH_3), 52.4 (CH_3). HRMS (FAB) m/z: Calcd for $C_{21}H_{18}NO_8$ $[M+H]^+$ 412.1032; Found: 412.1058.

Dimethyl 2-(tert-butyl)-5-phenylfuran-3,4-dicarboxylate (7c): MPLC: 18 min (hexane:AcOEt = 90:10). 71.3 mg (56%). Colorless oil. IR (neat) ν cm^{-1}; 1743, 1715, 1439, 1213. ^{1}H NMR (300 MHz) δ ppm; 7.85-7.75 (m, 2H; Ar-H), 7.51-7.37 (m, 3H; Ar-H), 3.87 (s, 3H; CH_3), 3.80 (s, 3H; CH_3), 1.40 (s, 9H; CH_3). ^{13}C NMR (75 MHz) δ ppm; 165.6 (C=O), 163.9 (C=O), 161.7 (C), 153.1 (C), 129.4 (CH), 129.2 (C), 128.3 (CH), 127.7 (CH), 114.1 (C), 113.6 (C), 52.3 (CH_3), 52.0 (CH_3), 34.2 (C), 28.5 (CH_3). HRMS (FAB) m/z: Calcd for $C_{18}H_{21}O_5$ $[M+H]^+$ 317.1389; Found: 317.1382.

Dimethyl 2-(4-chlorophenyl)-5-phenylfuran-3,4-dicarboxylate (7g): MPLC: 38 min (hexane:AcOEt = 95:5). 74.4 mg (50%). Colorless oil. IR (neat) ν cm^{-1}; 1728, 1487, 1221, 1092. ^{1}H NMR (300 MHz) δ ppm; 7.88-7.79 (m, 4H; Ar-H), 7.50-7.39 (m, 5H; Ar-H), 3.89 (s, 3H; CH_3), 3.88 (s, 3H; CH_3). ^{13}C NMR (75 MHz) δ ppm; 164.1 (C=O), 164.0 (C=O), 153.64 (C), 153.58 (C), 135.7 (C), 129.8 (CH), 129.1 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (C), 127.3 (CH), 117.41 (C), 117.39 (C), 52.5 (CH_3) (note that two carbon peaks overlap with each other). HRMS (FAB) m/z: Calcd for $C_{20}H_{16}ClO_5$ $[M+H]^+$ 371.0686; Found: 371.0693.

Acknowledgments ((optional))

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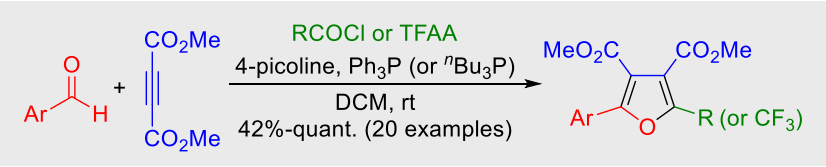

A combination of 4-picoline and Ph_3P (or $^nBu_3P$) efficiently promotes a formal [2+2+1] synthesis of tetrasubstituted furans from aldehydes, acetylenedicarboxylates and acyl compounds via O-acylation of the α,β-enone intermediates followed by intramolecular Wittig reaction under the metal-free and mild conditions. The present method can be applied not only to acyl chlorides but also trifluoroacetic anhydride as acyl compounds.

Multicomponent Annulation

*Keiichiro Tateishi, Yuri Matsumoto, Akio Saito**

Page No. – Page No.

Formal [2+2+1] Synthesis of Tetrasubstituted Furans from Aldehydes, Acetylenedicarboxylates and Acyl Compounds