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New Efficient Synthesis of 1,2,4-Trisubstituted Furans by a Sequential Passerini/Wittig/Isomerization Reaction Starting from Baylis–Hillman β-Bromo Aldehydes

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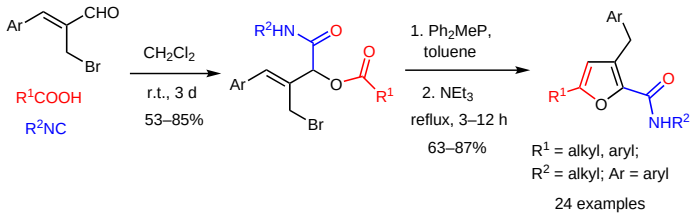

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Abstract A new and efficient synthesis of 1,2,4-trisubstituted furans from a Baylis–Hillman β-bromo aldehyde, an acid, an isocyanide, and methyl(diphenyl)phosphine, by a sequential Passerini condensation, Wittig reaction, and isomerization in the presence of triethylamine is reported.

Key words Passerini reaction, Wittig reaction, Baylis–Hillman reaction, furans, isomerization

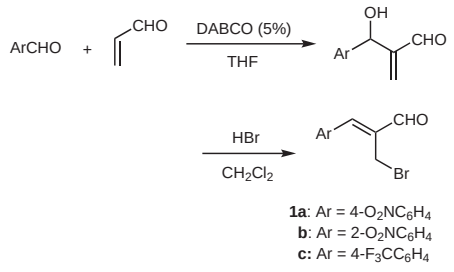
Isocyanide-based multicomponent reactions (IMCRs) have become powerful tools in organic and medicinal chemistry for diversity-oriented and complexity-generating syntheses of drug-like small molecules.[1] Among various IMCRs, the Passerini reaction and the Ugi reaction are two main examples which have been widely used in preparing various α-acyloxy or α-acylamino amide adducts in one operational step.[2] The so-called post-Passerini modifications have emerged as useful tools for the preparation of structurally diverse molecules, especially heterocyclic compounds.[3] For example, a domino Passerini/aldol reaction was recently used to prepare bicyclic isocoumarins with various substituted patterns through solvent-dependent pathways.[3a] An oxidation/Passerini/hydrolysis/alkylation strategy has been developed for the construction of triazolo-fused benzoxazepines with high operational simplicity.[3b] γ-Lactams and γ-lactones have also been obtained by sequential Passerini/ring-opening/cyclization reactions under acidic or basic conditions.[3c]

Furans are an important class of heterocycles that are present in many natural products and biologically active molecules. Some derivatives of this heterocycle were recently reported to show good anticancer activity,[4] antiamoebic activity,[5] selective protein arginine methyltransferase 1 inhibitory activity,[6] and cyclooxygenase-1 inhibitory activity.[7] Owing to the broad range of activities of furan derivatives, many attractive methods for their synthesis have been developed in the past few decades. Conventional methods such as the Paal–Knorr[8] and Feist–Benary[9] reactions have found wide application in furan synthesis. Polysubstituted furan derivatives have also been recently prepared by numerous metal-free intramolecular approaches,[10] or transition-metal-catalyzed synthetic strategies[11] involving, for example, copper, palladium, gold, silver, ytterbium, or ruthenium, with remarkable improvements.

The Wittig reaction has been recognized as one of the most powerful methods for constructing C=C double bonds, and it has become an efficient tool in organic chemistry for the preparation of alkenes.[12] The intramolecular Wittig reaction has been extensively used in the preparation of various heterocycles through intramolecular cyclization.[13] The combination of an Ugi or Passerini condensation with a subsequent Wittig reaction provides an efficient method for the synthesis of a series of biologically useful heterocycles. For example, Dömling and co-workers reported the synthesis of highly substituted butenolides, pyrrolidinones, and pyridones by sequential Ugi/Horner or Passerini/Horner reactions.[14] In our previous work, an Ugi or Passerini/Wittig sequence was used to prepare polysubstituted 1*H*-2-benzazepin-1-ones, 1*H*-isochromenes, isoquinolin-1(2*H*)-ones and indoles, starting from the corresponding phosphonium precursors.[15] Here, we report a new efficient synthesis of 1,2,4-trisubstituted furans by a sequential Passerini/Wittig/isomerization reaction sequence starting from Baylis–Hillman β-bromo aldehydes.

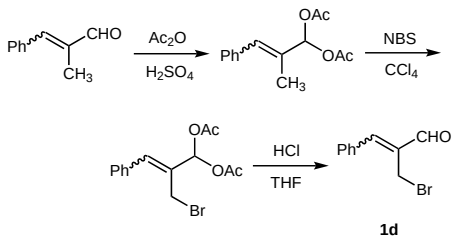
There are few reports on Baylis–Hillman reactions between acrylaldehyde and other aldehydes.[16] Our experimental results revealed that only reactive aromatic aldehydes ArCHO (Ar = 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 4-$F_3CC_6H_4$) gave the corresponding Baylis–Hillman adducts in 60–75% yields

(Scheme 1). Other aromatic aldehydes (Ar = 4-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 2-BrC_6H_4, Ph, 4-Tol, 4-$MeOC_6H_4$) gave only traces of the product, probably due to the preferential self-polymerization of acrylaldehyde under the reaction condition. The Baylis–Hillman β-bromo aldehydes **1a–c** were then obtained in 87–92% yield by further bromination of the corresponding Baylis–Hillman adducts.



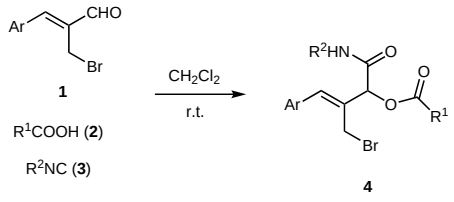
Scheme 1 Preparation of bromides **1a–c** by the Baylis–Hillman reaction

Although the 3-phenyl-substituted β-bromo aldehyde **1d** could not be obtained by a Baylis–Hillman reaction, it was successfully prepared by another synthetic route, starting from commercially available 2-methyl-3-phenylacrylaldehyde (Scheme 2).



Scheme 2 Preparation of bromide **1d**

With the β-bromo aldehydes **1a–d** in hand, we investigated their Passerini reactions. A mixture of the β-bromo aldehyde **1**, acid **2**, and isocyanide **3** was stirred in dichloromethane at room temperature for three days (Scheme 3). The Passerini reaction occurred smoothly, and the bromides **1** were found to be compatible with the reaction condition. The corresponding products **4** were finally obtained in 53–85% yields.[17]



Scheme 3 Passerini reaction for preparation of the bromides **4**

We initially examined the reaction of the Passerini product **4a** with triphenylphosphine, and we found that it readily gave the corresponding phosphonium salt at room temperature. Triethylamine was then added to the reaction mixture in an attempt to induce a further intramolecular Wittig reaction without isolation of the phosphonium salt intermediate. When the reaction mixture was stirred at room temperature, no product was detected (Table 1, entry 1). However, at reflux, a mixture of furan **5a** (38%, Table 1, entry 2) and furan-2(3*H*)-one **6a** (43%) was unexpectedly obtained. Changing the base from NEt_3 to DABCO, $NaHCO_3$, K_2CO_3, or Cs_2CO_3 gave lower yields of furan **5a** as the major product (Table 1, entry 3–6). No product was obtained when NEt_3/MeOH or NEt_3/DMSO was used (Table 1, entries 7 and 8), probably due to decomposition of the phosphonium salt intermediate in the more-polar solvent. A lower yield was also obtained when the NEt_3/THF system was used at the reflux (Table 1, entry 9). Adding an external oxidant to the reaction mixture had no obvious effect on the product ratios (Table 1, entries 10 and 11). When the reaction mixture was carried out under a nitrogen atmosphere, the furan **5a** was obtained exclusively in moderate yield (53%, Table 1, entry 12).

The structure of the unexpected product, the furan-2(3*H*)-one **6a**, was confirmed from its spectral data. Furthermore, a single crystal of **6a** was grown from the CH_2Cl_2/petroleum ether solution, and its proposed structure was verified by X-ray crystal analysis (Figure 1).[18]

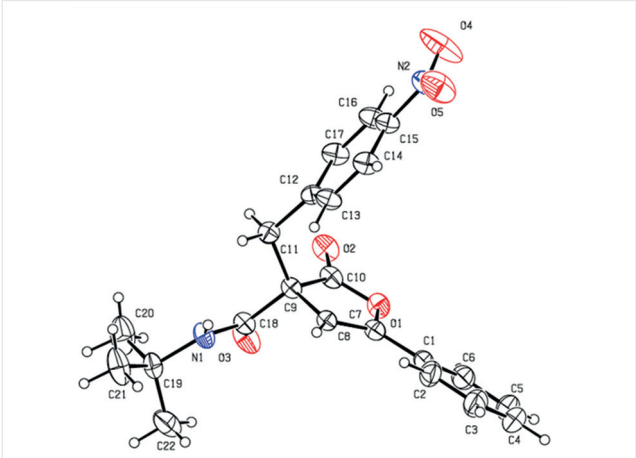
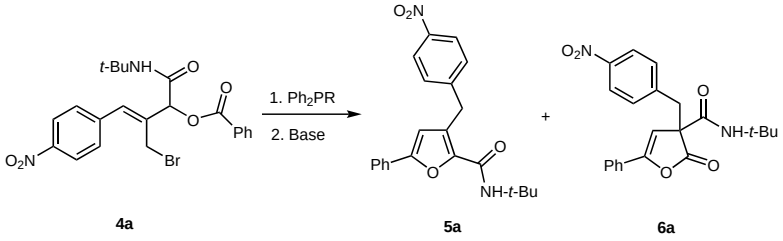


Figure 1 ORTEP drawing of **6a** with 50% probability thermal ellipsoids

The formation of the furan-2(3*H*)-one **6** (Scheme 4) might involves: (i) air oxidation of the sp^3-C–H bond of phosphonium salt **7** in the presence of NEt_3 to afford the key intermediate **8**, as reported in similar cases;[19] (ii) rearrangement of the intermediate **8** to **9** through migration of the carboxamide group to the vinyl carbon under the basic condition, in a manner similar to the rearrangement of benzilic acid with migration of the phenyl group to the car-

Table 1 Investigation of the Reaction Conditions



4a 5a 6a

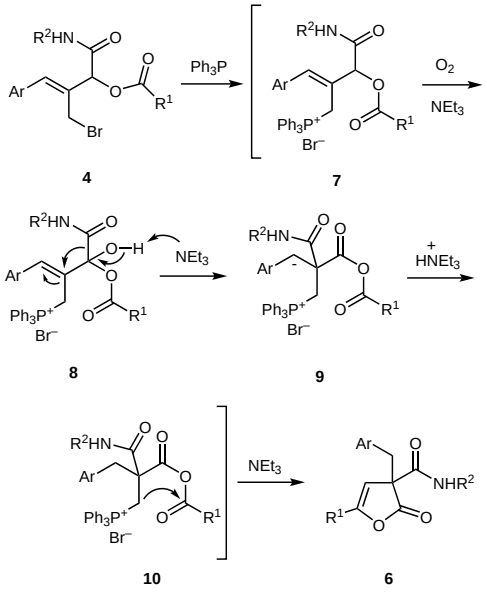
Entry	Phosphine	Solvent	Temp	Time (h)	Base	Additive	Yield (%)[a]	
							5a	**6a**
1	Ph_3P	toluene	r.t.	12	NEt_3	–	0	0
2		toluene	reflux	8	NEt_3	–	38	43
3		toluene	reflux	8	DABCO	–	37	30
4		toluene	reflux	8	$NaHCO_3$	–	25	10
5		toluene	reflux	8	K_2CO_3	–	35	14
6		toluene	reflux	8	Cs_2CO_3	–	27	10
7		MeOH	reflux	6	NEt_3	–	0	0
8		DMSO	90 °C	6	NEt_3	–	0	0
9		THF	reflux	8	NEt_3	–	28	25
10		toluene	reflux	8	NEt_3	CrO_3	31	34
11		toluene	reflux	8	NEt_3	H_2O_2	30	33
12		toluene	reflux[b]	8	NEt_3	–	53	0
13	Ph_2PMe	toluene	reflux	4	NEt_3	–	82	0
14	Me_3P	toluene	reflux	2	NEt_3	–	45	0

[a] Isolated yield based on the bromide **4a**.
[b] Under N_2.

bonyl carbon;[20] (iii) proton transfer of **9** to produce phosphonium salt **10**; and (iv) an intramolecular Wittig reaction of **10** in the presence of NEt_3, through the reactive anhydride carbonyl group, to give furan-2(3*H*)-one **6**.

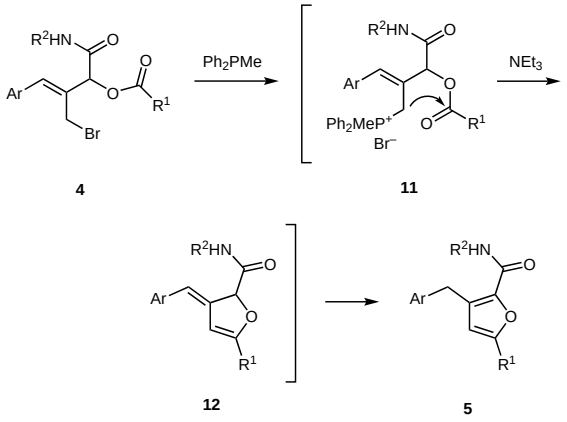
We speculated that if the phosphine reagent was changed from Ph_3P to Ph_2MeP, a more reactive Wittig reagent might result, and furans **5** might be formed predominately. Indeed, as shown in Table 1, entry 13, furan **5a** was produced exclusively in a good yield (82%) when Ph_2MeP was utilized as the phosphine reagent, even without the protection of a N_2 atmosphere. However, when Me_3P was used, the reaction mixture became more complex, and a moderate yield (45%) of the product was obtained probably due to the presence of side reactions (Table 1, entry 14).

Having determined the optimal conditions (entry 13), we examined the reactions of various Passerini products **4** with Ph_2MeP as the phosphine reagent (Table 2). All reactions proceeded smoothly in refluxing toluene to give moderate to good yields (63–87%) of furans **5** with various substituents (Table 2).[21] Good yields of compounds **5a–s** (71–87%) were obtained with R^1 being an aromatic group with



Scheme 4 A possible mechanism for the formation of **6**

Table 2 One-Pot Preparation of Furans **5** by Using Ph_2MeP as the Phosphine Reagent. Preparation and Yields of Compounds **5a–x**



Product	Ar	R^1	R^2	Yield[a] (%)
5a	4-$O_2NC_6H_4$	Ph	*t*-Bu	82
5b	4-$F_3CC_6H_4$	Ph	Bu	87
5c	4-$O_2NC_6H_4$	Ph	Bu	76
5d	2-$O_2NC_6H_4$	Ph	*t*-Bu	84
5e	4-$O_2NC_6H_4$	4-ClC_6H_4	*t*-Bu	75
5f	4-$O_2NC_6H_4$	4-ClC_6H_4	Bu	77
5g	4-$O_2NC_6H_4$	4-FC_6H_4	Bu	83
5h	Ph	4-FC_6H_4	*t*-Bu	85
5i	4-$O_2NC_6H_4$	4-Tol	*t*-Bu	77
5j	2-$O_2NC_6H_4$	4-Tol	Bu	74
5k	4-$O_2NC_6H_4$	4-Tol	Bu	71
5l	2-$O_2NC_6H_4$	4-Tol	*t*-Bu	75
5m	4-$F_3CC_6H_4$	4-$MeOC_6H_4$	*t*-Bu	78
5n	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	*t*-Bu	72
5o	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	Cy	70
5p	Ph	4-$MeOC_6H_4$	*t*-Bu	77
5q	2-$O_2NC_6H_4$	4-$F_3CC_6H_4$	Bu	85
5r	2-$O_2NC_6H_4$	2-FC_6H_4	*t*-Bu	78
5s	2-$O_2NC_6H_4$	3-$O_2NC_6H_4$	*t*-Bu	86
5t	Ph	Et	*t*-Bu	75
5u	2-$O_2NC_6H_4$	Et	*t*-Bu	81
5v	2-$O_2NC_6H_4$	*i*-Pr	*t*-Bu	71
5w	4-$O_2NC_6H_4$	*t*-Bu	Bu	63
5x	4-$O_2NC_6H_4$	4-$ClC_6H_4CH_2$	*t*-Bu	75

[a] Isolated yield based on bromide **4**.

electron-donating (MeO or Me) or electron-withdrawing substituent (F, Cl, CF_3, or NO_2) on the benzene ring. When R^1 was an alkyl group, moderate to good yields of products **5t–x** (63–81%) were obtained. It is noteworthy that a 63% yield of compound **5w** was obtained when R^1 was a bulky *t*-Bu group. The formation of furans **5** can be rationalized in terms of an initial reaction of bromide **4** with Ph_2MeP to give the phosphonium salt **11**. Further intramolecular Wittig reaction of **11** produces dihydrofuran **12**, which isomerizes through a 1,3-H shift in the presence of NEt_3 to give furan **5**.

In conclusion, a Passerini/Wittig/isomerization sequence, starting from Baylis-Hillman β-bromo aldehydes, for preparing 1,2,4-trisubstituted furans is reported. The method was adapted to the synthesis of various substituted furans under mild reaction condition, which makes it useful in synthetic and medicinal chemistry. The unexpected formation of furan-2(3*H*)-one **6a** was observed when Ph_3P was used as the phosphine reagent.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588564.

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(17) **1-(Aminocarbonyl)-3-aryl-2-(bromomethyl)prop-2-en-1-yl Esters 4; General Procedure**

The appropriate acid **2** (2 mmol) and isocyanide **3** (2 mmol) were added to a solution of the Baylis–Hillman β-bromo aldehyde **1** (2 mmol) in CH_2Cl_2 (4 mL), and the mixture was stirred at r.t. for 3 d until the reaction was complete (TLC). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography [silica gel, EtOAc/PE (1:10)].

(2*Z*)-2-(Bromomethyl)-1-[(*tert*-butylamino)carbonyl]-3-(4-nitrophenyl)prop-2-en-1-yl Benzoate(4a)

White solid; yield: 664 mg (70%); mp 118–120 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.2 Hz, 2 H, Ar-H), 8.13 (d, *J* = 5.4 Hz, 2 H, Ar-H), 7.62–7.51 (m, 5 H, Ar-H), 7.07 (s, 1 H, =CH), 6.27 (s, 1 H, NH), 6.03 (s, 1 H, CH), 4.26 (d, *J* = 10.8 Hz, 1 H, CH_2^a), 4.16 (d, *J* = 10.2 Hz, 1 H, CH_2^b), 1.41 (s, 9 H, $3CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.0, 164.5, 147.1, 141.5, 135.4, 133.9, 133.3, 129.8, 129.6, 128.7, 123.8, 75.8, 51.8, 28.5, 27.1. HRMS: *m/z* [M + H]$^+$ calcd for $C_{22}H_{24}BrN_2O_5$: 475.0863; found: 475.0860.

(18) CCDC 1545270 contains the supplementary crystallographic data for compound **6a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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(21) **Furans 5; General Procedure**

In an oven-dried flask, bromide **4** (1 mmol) and Ph_2MeP (0.20 g, 1 mmol) were dissolved in toluene (5 mL) at r.t. After two hours, the white phosphonium salt solid **11** formed. Without isolation of the phosphonium salt intermediate, NEt_3 (0.20 g, 2 mmol) was added and the mixture was stirred at reflux for 3–12 h until the reaction was complete (TLC). The solution was then concentrated under reduced pressure and the residue was purified by flash chromatography [silica gel, EtOAc/PE (1:12 to 1:1)].

***N*-(*tert*-Butyl)-3-(4-nitrobenzyl)-5-phenyl-2-furamide (5a)**

Light-yellow oil; yield: 309 mg (82%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.53 (d, *J* = 7.2 Hz, 2 H, Ar-H), 7.39–7.23 (m, 5 H, Ar-H), 6.37 (s, 1 H, furan-4-H), 6.21 (s, 1 H, NH), 4.31 (s, 2 H, CH_2), 1.43 (s, 9 H, $3CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.8, 153.5, 147.9, 146.4, 142.0, 130.1, 129.5, 129.2, 128.7, 128.6, 124.3, 123.6, 109.0, 51.4, 31.3, 29.0. HRMS: *m/z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2O_4$: 379.1652; found: 379.1653.