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DABCO-Catalyzed Reaction of α-Halo Carbonyl Compounds with Dimethyl Acetylenedicarboxylate: A Novel Method for the Preparation of Polysubstituted Furans and Highly Functionalized 2*H*-Pyrans

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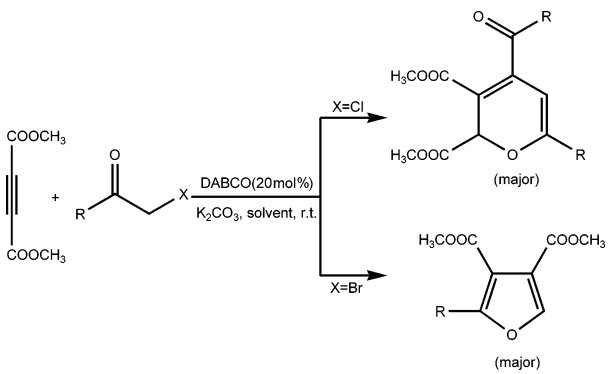
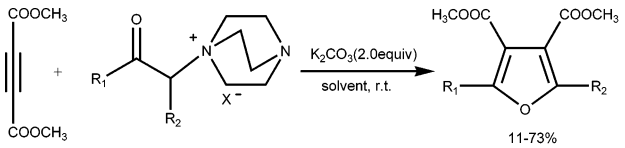


Polysubstituted furans and highly functionalized 2*H*-pyrans were prepared in good yields by DABCO-catalyzed reactions of α-halo carbonyl compounds with dimethyl acetylenedicarboxylate (DMAD) at room temperature.

Furan and pyran are important building blocks in many natural compounds having important biological activities[1,2]and are also widely used as intermediates in organic and pharmaceutical synthesis.[3,4] These facts have led to the exploring of new methods for the synthesis of polysubstituted furans and highly functionalized pyrans.[5,6] We work in this field and have recently reported a novel method for the synthesis of polysubstituted furans via an ammonium ylide route.[7] Based on our research, the various polysubstituted furans were obtained by the reaction of dimethyl acetylenedicarboxylate (DMAD) with ammonium ylides in the presence of anhydrous K_2CO_3 at room temperature (Scheme 1). This procedure was then extended to a "one-pot" and catalytic process (Scheme 2). For better understanding of the mechanism and the scope of application of this type of reaction, α-chloro-2-acetylthiophene **2a** was chosen as reactant for the model reaction to optimize reaction conditions. DMAD was treated with 2.0 equiv of **2a** in the presence of 20 mol % of DABCO and 2.0 equiv of anhydrous K_2CO_3 in various solvents at room temperature. We surprisingly found that a new ring adduct **4a** was formed as a major product along with the formation of a small amount of the polysubstituted furan **3a** in

SCHEME 1



R_1=Ph, *p* -Br-Ph, *p*-CH_3-Ph, *p*-CH_3O-Ph, thiophenyl, 4-bromothiophenyl, pyridinyl, CH_3, $(CH_3)_3C$, Fc
R_2=H, CH_2CH_3, $COOCH_2CH_3$, X=Cl or Br

SCHEME 2

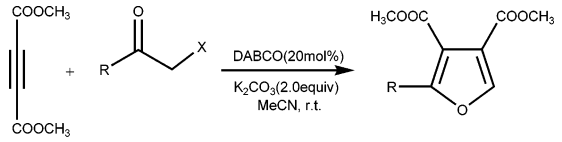


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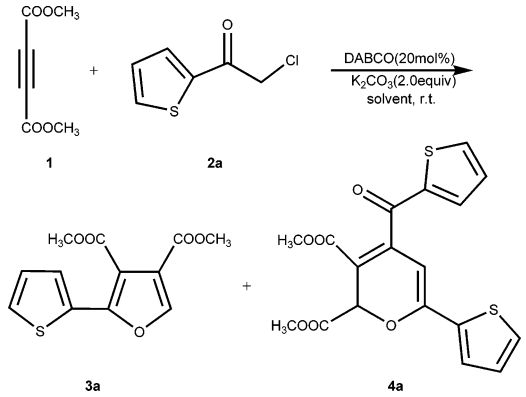
TABLE 1. Reactions of α-Chloroketone 2a with DMAD Catalyzed by DABCO in Various Solvents



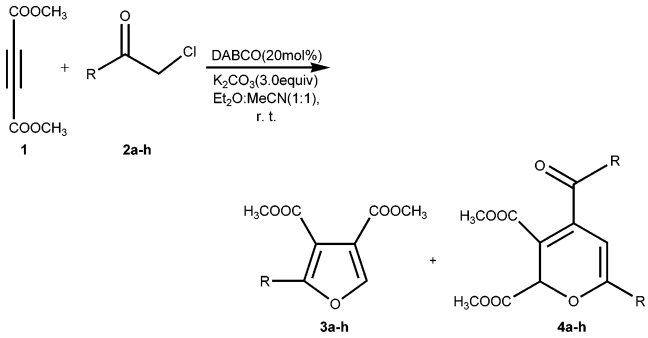
			product (yield, %)[c]	
entry	solvent	time, h	**3a**	**4a**
1	CH_2Cl_2	6[a]	10	37
2	MeCN	2	19	36
3	Et_2O	24[a]	7	12
4	DMSO	2	22	14
5	THF	6[b]	6	14
6	MeCN/Et_2O (1:1)	4	19	62
7	MeCN/THF (1:1)	3	22	48

[a] Heat to reflux. [b] Heat to 50 °C. [c] Isolated yields.

various solvents (Table 1), which is obviously different from the results we obtained previously via the reaction between the quaternary ammonium salt of α-chloro-2-acetylthiophene and DMAD.[7] From the results we can see that the reactions proceeded very slowly in CH_2Cl_2, Et_2O, and THF at room temperature and the reaction mixture needed to be heated to get moderate yields (entries 1, 3, and 5). In MeCN and DMSO, although the reactions completed within 2 h, low yields were observed because of the formation of many byproducts (entries 2 and 4). The reaction in mixed solvents, such as MeCN/Et_2O (1:1), MeCN/THF (1:1), and especially MeCN/ Et_2O (1:1) (entry 6), was better than the other ones and needed no heating or long reaction time to give good yields. So MeCN/Et_2O (1:1) was chosen as the most effective solvent for the reactions of α-chloroketones with DMAD at room temperature.

Then we examined the reaction of various α-chloroketones with DMAD under the chosen reaction conditions. To enhance the selectivity, we used an excess of α-chloroketones (3.0 equiv) and anhydrous K_2CO_3 (3.0 equiv) with the intention to get 2*H*-pyran derivatives exclusively. All results are summarized in Table 2. In the presence of a catalytic amount of DABCO (20 mol %) and K_2CO_3 (3.0 equiv) in MeCN/Et_2O (1:1) at room temperature, 2*H*-pyran derivatives **4** rather than expected furans **3** were formed as major products (entries **2a**−**e**, **2g**, **2h**). Only for **2f**, furan derivatives **3f** and 2*H*-pyran derivatives **4f** were produced almost equally. In most cases, the generation of furan **3** and 2*H*-pyran **4** was not greatly effected by changes in the R group except that when R was changed to a large group, a lower yield was obtained because of the steric hindrance (entries **2g** and **2h**). The structures of furan **3** and 2*H*-pyran **4** were determined by NMR spectra, MS, HRMS data of all compounds, and X-ray diffraction for **3c**[8] and **4e**.[9]

TABLE 2. Reactions of DMAD with Various α-Chloroketones



entry	R	time, h	product (yield, %)[a]	
2a	thiophen-2-yl	4	**3a** (19)	**4a** (62)
2b	5-bromothiophen-2-yl	6	**3b** (19)	**4b** (39)
2c	Ph	2	**3c** (24)	**4c** (57)
2d	*p*-Br-Ph	3	**3d** (19)	**4d** (56)
2e	*p*-CH_3-Ph	2	**3e** (28)	**4e** (60)
2f	*p*-CH_3O-Ph	2	**3f** (48)	**4f** (41)
2g	2,4-dimethylbenzenyl	6	**3g** (18)	**4g** (23)
2h	1,2,3,4-terthydro-naphthalen-5-yl	5	**3h** (28)	**4h** (39)

[a] Isolated yields.

To test this strategy for the synthesis of polysubstituted furans exclusively, we used α-bromoketones instead of α-chloroketones in this process and got excellent results using CH_2Cl_2 as a solvent. In the reaction of DMAD with α-bromoketones (2.0 equiv) in the presence of 20 mol % of DABCO and 2.0 equiv of anhydrous K_2CO_3 in CH_2Cl_2 at room temperature, trace or no 2*H*-pyran was produced. We got polysubstituted furans in good to excellent yields exclusively (Table 3). Comparing the results obtained from α-bromoketones and α-chloroketones, we can choose different α-halo carbonyl compounds, α-bromo or α-chloro, to get different products, pyrans or furans, according to our requests.

We also used this method in the synthesis of tetrasubstituted furans and got good results as well. For example, α-bromoketone **2q** reacted with DMAD in the presence of 20 mol % of DABCO and 2.0 equiv of anhydrous K_2CO_3 in toluene under reflux, giving a moderate yield of the tetrasubstituted furan **3i**, which can be efficiently transformed to a tetrahydrofuran lignan[10] (Scheme 3).

When the procedures described above were conducted using α-halo ester, acid, or acetylamine to obtain furans

(8) **Crystal data for 3c**: $C_{14}H_{12}O_5$, mp 68−70 °C; chemical formula weight 260.24; monoclinic space group *P*2(1)/*c*, a = 14.698(2), b = 11.720(1), c = 7.3105(7) Å; α = 90.00°, β = 97.916(9)°, γ = 90.00°, V = 1247.3(2) Å^3. T = 290(2) K, Z = 4, D_c = 1.386 Mg/m^3, μ = 0.106 mm^{-1}, λ = 0.71073 Å, F (000) 544, crystal size 0.52 × 0.48 × 0.48 mm^3, 2255 independent reflections [R(int) = 0.0122]; reflections collected 2690; refinement method, full-matrix least-squares on F^2; goodness-of-fit on F^2 1.073; final R indices [$I > 2\delta(I)$] R_1 = 0.0383, wR_2 = 0.1038, R indices (all data) R_1 = 0.0524, wR_2 = 0.0138. Extinction coefficient 0.126(7). Largest diff. peak and hole 0.173 and −0.163 e Å^{-3}.

(9) **Crystal data for 4e:** $C_{24}H_{22}O_6$, mp 148−150 °C; chemical formula weigh 406.42; monoclinic space group *P*2(1)/*c*, a = 7.468(2), b = 19.811(5), c = 14.249(4) Å; α = 90.00°, β = 96.801(4)°, γ = 90.00°, V = 2093.2(10) Å^3. T = 291(2) K, Z = 4, D_c = 1.290 Mg/m^3, μ = 0.093 mm^{-1}, λ = 0.71073 Å, F (000) 856, crystal size 0.56 × 0.45 × 0.34 mm^3, 3872 independent reflections [R(int) = 0.0168]; reflections collected 10796; refinement method, full-matrix least-squares on F^2; goodness-of-fit on F^2 1.102; final R indices [$I > 2\delta(I)$] R_1 = 0.0370, wR_2 = 0.1028, R indices (all data) R_1 = 0.0448, wR_2 = 0.1064. Extinction coefficient 0.0088(13). Largest diff. peak and hole 0.171 and −0.146 e Å^{-3}.

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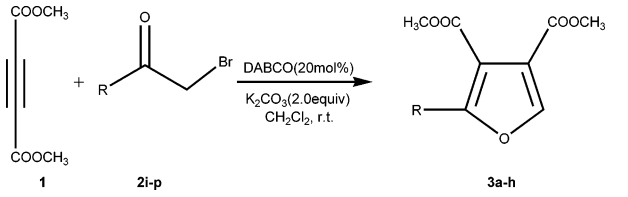
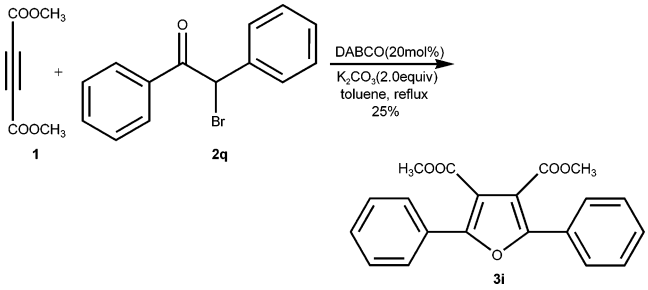
TABLE 3. Reactions of DMAD with Various α-Bromoketones



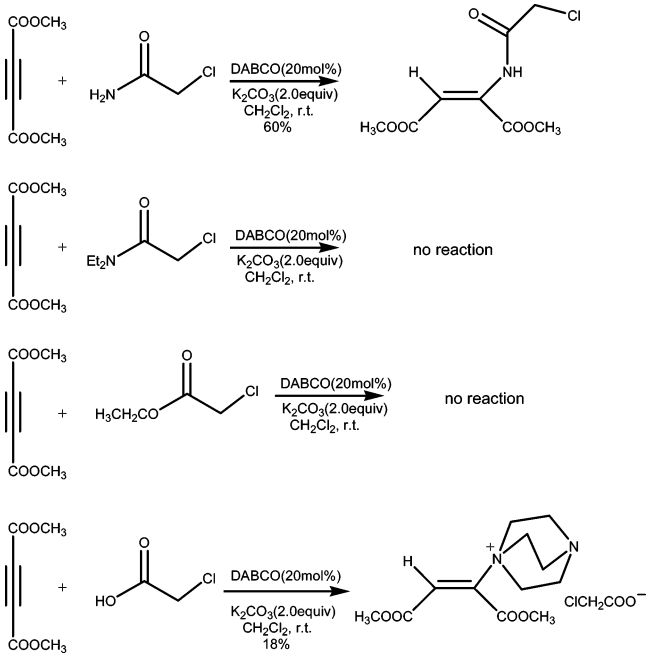
entry	R	time, h	product (yield, %)[a]
2i	thiophen-2-yl	4	**3a** (78)
2j	5-bromothiophen-2-yl	6	**3b** (33)
2k	Ph	3	**3c** (83)
2l	*p*-Br-Ph	3	**3d** (89)
2m	*p*-CH_3-Ph	3	**3e** (92)
2n	*p*-CH_3O-Ph	4	**3f** (57)
2o	2,4-dimethylbenzenyl	4	**3g** (64)
2p	1,2,3,4-terthydro-naphthalen-5-yl	5	**3h** (67)

[a] Isolated yields.

SCHEME 3



SCHEME 4



or 2*H*-pyrans, the method becomes invalid. Only addition products were observed in some cases (Scheme 4).

It is worthy to note that these reactions do not take place in the absence of DABCO, which suggests that the tertiary amine is required as a catalyst in this procedure. On the basis of above observations and previous investigations,[11,12] a plausible mechanism for the reaction of α-halo carbonyl compounds with DMAD is outlined in Scheme 5. In this process, a α-halo carbonyl compound **2** undergoes S_N2 displacement with tertiary amine DABCO to give a quaternary ammonium salt **a.** Deprotonation of **a** with mild base (anhydrous K_2CO_3) forms the ylide **b**, which undergoes Michael addition to DMAD to give intermediate **c**. On the one hand, intermediate **c** undergoes a [1,3] acyl migration to form an ylide intermediate **d**. Then the facile enolation takes place to give furan **3** by a cyclization reaction and regenerates the catalyst DABCO. On the other hand, intermediate **c** undergoes a [1,-3] proton migration to form another ylide intermediate **f**, which undergoes S_N2 displacement with a second molecule of the α-halo carbonyl compound to give a quaternary ammonium salt **g**. Deprotonation and then enolization of **g** in the presence of anhydrous K_2CO_3 form intermediate **h.** The enolate oxygen of **h** attacks nucleophilically the other DMAD carbon to generate the 2*H*-pyran **4** with recycling of DABCO. In the reaction of α-bromoketone with DMAD, the low yield of 2*H*-pyran **4** may be ascribed to the steric hindrance of the bromide atom. It is difficult for the sterically more hindered α-bromoketone to undergo S_N2 displacement in the transformation of **f** to **g**, formation of furan **3** then proceeding faster than the formation of 2*H*-pyran **4**. The sterically less hindered α-chloroketones showed opposite reactivities. So 2*H*-pyran derivatives **4** and furan derivatives **3** were formed as major products in the reactions of α-chloroketones and α-bromoketone with DMAD, respectively.

In conclusion, we have developed a convenient method for the synthesis of polysubstituted furans and highly functionalized 2*H*-pyrans. In view of the mild reaction conditions and the availability of the starting materials, this procedure should be suited for the preparation of sensitive furans and highly functionalized 2*H*-pyrans on a large scale. Further studies are under way in our laboratory to extend this mild annulation strategy to synthesis of other classes of heteroromatic compounds.

Experimental Section

Using 2a as Example. DABCO (0.1 mmol) was added to a stirred solution of **2a** (1.5 mmol) in 6 mL of MeCN/Et_2O (1:1), and the mixture was stirred at room temperature (25−30 °C) for 30 min. Anhydrous K_2CO_3 (1.5 mmol) was added, followed by dimethyl acetylenedicarboxylate (0.5 mmol). The reaction was stirred at room temperature until thin layer chromatographic analysis showed complete consumption of the dimethyl acetylenedicarboxylate. H_2O (10 mL) was added to the mixture and extracted thrice with 15 mL of CH_2Cl_2. The combined extracts were washed with H_2O and brine and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica column to give the 2*H*-pyran **4a**.[13]

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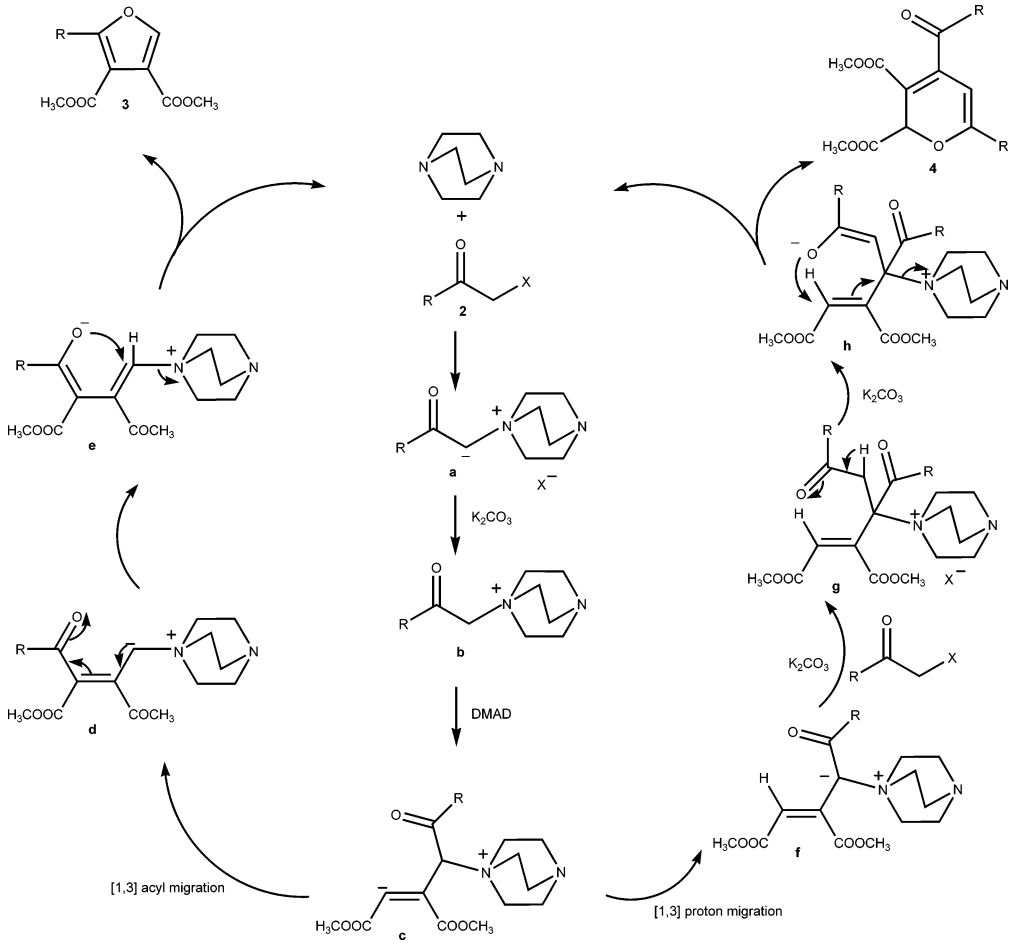
(13) **Spectral data for 4a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59(s, 3H), 3.78(s, 3H), 5.94(s, 1H), 6.01(s, 1H), 7.07−7.13(m, 2H), 7.47(d, J = 4.8 Hz, 1H), 7.53(d, J = 2.7 Hz, 1H), 7.61(d, J = 3.9 Hz, 1H), 7.72(d, J = 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.3, 53.2, 72.5, 97.6, 110.8, 128.5, 128.7, 128.8, 130.2, 134.6, 135.3, 136.0, 142.8, 144.6, 154.6, 164.0, 169.8, 187.0. IR (KBr) ν 2953, 1741, 1710, 1658, 1412, 1254, 1086, 756 cm^{-1}. MS *m/z* (%) 390(M^+, 2.92), 359(0.79), 331(52.84), 111-(100). HRMS calcd for $C_{18}H_{14}O_6S_2$ (M + NH_4) 408.0570, found 408.0567.

SCHEME 5



Other detailed experimental procedures are presented in Supporting Information.

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Supporting Information Available: Experimental procedures and spectral data of all compounds and single-crystal X-ray crystallographic data for compounds **3c** and **4e** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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