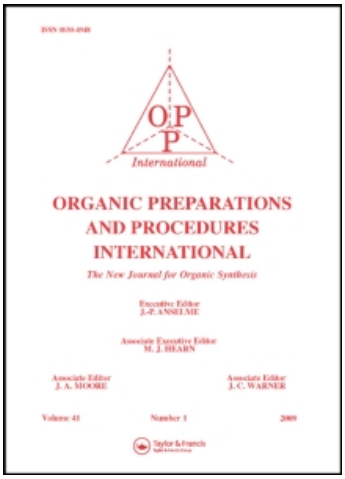

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AN EFFICIENT ONE-POT SYNTHESIS OF 2-AMINO-4*H*-PYRANS

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AN EFFICIENT ONE-POT SYNTHESIS OF 2-AMINO-4*H*-PYRANS

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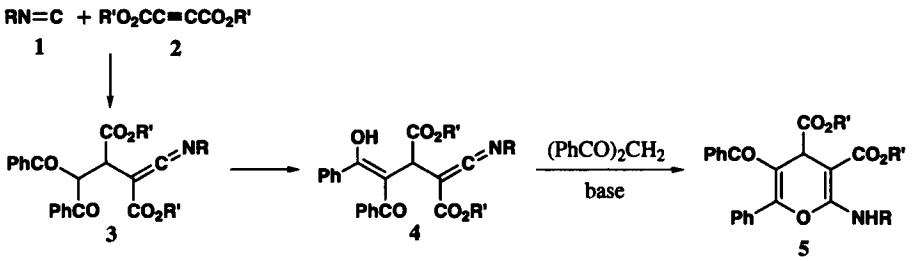
2-Amino-4*H*-pyrans are an important group of compounds with various applications. Some have been shown to exhibit biological activity and have been used as anti-cancer, anti-hypertensive and coronary dilating agents.[1-3] They are also important intermediates in organic synthesis.[4-9] A number of different methods for the synthesis of 2-amino-4*H*-pyran derivatives have been described.[10-16] We now report a one-pot synthesis of dimethyl, diethyl and di-*tert*-butyl-2-(*tert*-butylamino)-5-benzoyl-6-phenyl-4*H*-pyran-3,4-dicarboxylate (**5a-c**) and of dimethyl, diethyl, di-*tert*-butyl-2-(cyclohexylamino)-5-benzoyl-6-phenyl-4*H*-pyran-3,4-dicarboxylates (**5d-f**) in fairly high yields. One of us has already reported the reaction between alkyl isocyanides (**1**) and dialkyl acetylenedicarboxylates (**2**) in the presence of 1,3-diphenylpropane-1,3-dione to afford the highly functionalized ketenimines **3**.[17] Reflux of these ketenimines in benzene for 2-3 days led only enolization to compounds **4** without cyclization. By changing the addition sequence of the reactants and using the suitable base, we have achieved the preparation of 2-amino-4*H*-pyrans (**5a-f**) in good yields (*Scheme 1*).



a) R = *t*-Bu, R' = Me; b) R = *t*-Bu, R' = Et; c) R = *t*-Bu, R' = *t*-Bu; d) R = Cyclohexyl, R' = Me; e) R = Cyclohexyl, R' = Et; f) R = Cyclohexyl, R' = *t*-Bu

Scheme 1

The ketenimines **3** were detected by IR spectroscopy in the early stage of this reaction as intermediates by following the appearance of the C=C=N absorption band at near 2060 cm^{-1}. For example during the synthesis of **5a**, the intensity of this absorption reached to its

maximum intensity after 40 min, and for the next 20 minutes there was no increase thus indicating that the formation of the intermediate **3a** was complete. At this stage, addition of a base and refluxing the reaction mixture converted the ketenimines to the final products **5a-f**. The appearance of the absorption bands during the formation of the ketenimines **3a-f**, as well as the total time for completion of the reaction and formation of the compounds **5a-f** are illustrated in *Table 1*. Since nearly the same results were obtained with piperidine, pyridine and triethylamine,[18] we report the reaction using triethylamine as the base because the purification

Table 1. Absorption bands (C=C=N), t_1 **4** and t_P **6**

	ν (**4**)	t_1 (**4**)	t_P (**6**)	Solvent
a	2061.8	40	120	CH_2Cl_2
b	2060.7	60	200	*p*-xylene
c	2059.9	40	160	*p*-xylene
d	2061.6	40	140	CH_2Cl_2
e	2060.5	60	200	*p*-xylene
f	2060.8	40	160	*p*-xylene

ν : cm^{-1} t_1, t_P: min

t_1 : The time for completing the synthesis of intermediate **4**.

t_P : The total time for completing the synthesis of product **6**.

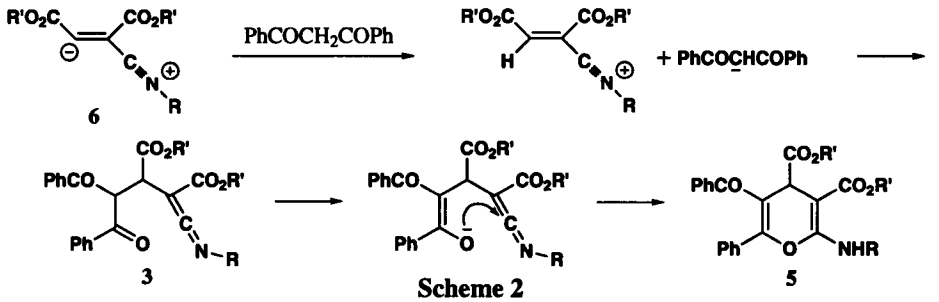
process was simpler. In addition to dichloromethane, other solvents such as benzene, toluene and *p*-xylene were also investigated (*Table 2*).

Table 2. Effect of Solvents on the Yields (%) of **6a-f** using Triethylamine (Et_3N)

6	CH_2Cl_2	C_6H_6	Toluene	*p*-Xylene
a	59	62	67	71
b	——	——	60	68
c	60	65	69	74
d	63	70	76	82
e	——	——	52	66
f	63	67	71	76

A possible mechanism for the formation of intermediates **3** and products **5** is shown in *Scheme 2*. Addition of the alkyl isocyanide to the acetylenic ester to generate the 1:1 adduct **6,** followed by protonation by 1,3-diphenylpropane-1,3-dione. The ketenimine **3** was formed upon attack of the anion of 1,3-diphenyl-1,3-propanedione to positively charged adduct of **7**. The ketenimine **3** has an acidic proton which is deprotonated by using a base (triethylamine) and converted in to **5**. The products were purified by column chromatography of silica gel and co-solvent ethyl acetate-*n*-hexane (1:3). Although the results were relatively good, a portion of prod-

ucts changed during the purification (ring closure) and the yields decreased to 60%. We succeeded in increasing the yields by using a mixture of water-acetone for the precipitation and crystallization of the products. Consequently, after the reaction was completed (as deduced by IR spectroscopy) and the solvents were removed under reduced pressure, the products were obtained pure in high yields by using a mixture of water-acetone .



Scheme 2

Structures **5** were assigned based on their elemental analyses and IR, UV, ^{1}H NMR, ^{13}C NMR and mass spectral data. The mass spectra of these compounds **5a-f** displayed molecular ion peaks at the appropriate m/z values which were not very intense probably due to two ester groups in the products. Initial fragmentation involved the loss of the 4*H*-pyran side-chains (CO_2R', HCO_2R', R, R'OH, PhCO, and Ph) and scission of the rings; the fragment m/z =105 ($PhCO^+$) was the base peak. The ^{1}H NMR spectrum of **5a** showed five sharp singlets, except for the phenyl protons region, readily recognizable as arising from *tert*-butyl (δ 1.41), two methoxy (δ 3.53, 3.74), methyne (δ 4.84), three multiplets (δ 7.17-7.23, 7.32-7.34, 7.68-7.68) for ten phenyl protons and a singlet signal at δ 8.82 for the amine group which appears upfield as a result of the presence of electron-withdrawing groups in the molecule and the rigid of 4*H*-pyran ring. The ^{1}H NMR spectra of **5d-f** were similar to that of **5a**, except for the signals of the cyclohexyl and ester groups. In addition, the NH group of **5d-f** appeared as a doublet with proton-proton coupling constant J = 8.045-8.641 Hz. Its ^{13}C NMR spectrum displayed absorptions in agreement with structure **5a**, only resonance of C_3 ($^{13}C{=}CO_2Me$) is more shielded than expected as a result of electron pairs resonance of N, O atoms at the a-position to this carbon in the 4*H*-pyran ring. Partial assignments of these resonances are given in the Experimental Section. The ^{13}C spectral data for compounds **5b-f**, were consistent with the proposed structures. Their IR spectra showed the N-H absorption (3248-3280 cm^{-1}), two sharp carbonyl absorptions (1724-1744, 1674-1693 cm^{-1}) and three sharp C-O absorptions. Their ultraviolet spectra in C_2H_5OH showed two maxima. One above λ = 199 nm with log ε = 4.99 - 4.82 and another above λ = 250 nm with log ε = 4.56-4.82.

The reaction described here represent a simple and efficient entry into the synthesis of highly functionalized 2-amino-4*H*-pyran-3,4-dicarboxylates with potential biological activities. Further investigations of this method are currently in progress to establish its scope and utility.

EXPERIMENTAL SECTION

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Columns chromatography was performed on silica gel (0.015-0.04 mm, mesh-size) and TLC on precoated plastic sheets ($25DC_{UV-254}$) respectively. Melting points were measured on Gallenkamp melting points apparatus and were not corrected. Elemental analysis for C, H and N were performed using a Heraeus-CHN-O-rapid analyzer.IR spectra were measured on a Shimadzu FT-IR-4300 spectro-photometer as KBr discs. ^{1}H and $^{13}CNMR$ spectra were recorded on a Bruker 500 MHz spectrometer in $CDCl_3$ solution and chemical shifts were recorded in ppm units by using $SiMe_4$ as internal standard. UV spectra were recorded in EtOH on Shimadzu UV-Visible 2100 spectrometer. Mass spectra were recorded on a Finnegan-MAT 8430 spectrometer at an ionization potential of 70ev.

Dimethyl 2-(*tert*-Butylamino)-5-benzoyl-6-phenyl-4*H*-pyran-3,4-dicarboxylate (5a).

Typical Procedure.- To a magnetically stirred solution of *t*-butylisocyanide (0.416 g, 5 mmol) and dimethyl acetylenedicarboxylate (0.71 g, 5 mmol) in 20 mL of the solvent (*Table 2*) (20 mL) a mixture of 1,3-diphenylpropane-1,3-dione (1.12 g, 5 mmol) in *p*-xylene (10 mL) was added dropwise at –10°C over 20 min. Following the reaction with IR spectroscopy showed absorption band of ketenimine (C=C=N) at 2062 cm^{-1}. When this band remained unchanged in further IR spectras, the reaction mixture was allowed to warm up to room temperature and was refluxed in the presence of triethylamine (0.01 g, 1 mmol), until the C=C=N absorption band was disappeared (*Table 1*). The solvent was removed under reduced pressure and the residue was purified by column chromatography using ethyl acetate-hexane (1:3) as eluent. The product was obtained as white crystals to yield 1.60 g (71%) of **5a**, mp 111-113°C. The product was recrystallized from water-acetone as co-solvent. The same procedure was used to prepare for **5b-f**. *Table 3* shows the yields, melting points and elemental analysis of **5a-f** and spectroscopic data of **5a-f** are given in *Table 4*.

Table 3. Yields, mps and Elemental Analysis of **5a-f**

Cmpd	Yields (%)	mp (°C)	Color	Elemental Analysis (Found) C	H	N
6a	71	111-113	white	69.46(69.44)	6.06(6.04)	3.12(3.21)
6b	68	112-114	yellow	70.40(70.39)	6.55(6.53)	2.93(3.01)
6c	72	148-150	yellow	72.00(71.97)	7.37(7.35)	2.63(2.64)
6d	82	129-130	white	70.66(70.63)	6.15(6.13)	2.94(2.97)
6e	66	122-124	yellow	71.54(71.50)	6.61(6.60)	2.87(2.91)
6f	74	159-161	yellow	72.96(72.94)	7.40(7.42)	2.50(2.46)

Table 4. ^{1}H NMR, ^{13}C NMR and MS Spectroscopic Data of **5a-f**

Cmpd	^{1}HNMR (δ:ppm)	^{13}CNMR (δ:ppm)	MS (m/z Fragment)
5a	1.41 (s, 9H, CMe_3) 3.53, 3.74 (2s, 6H, $2CH_3O$) 4.84 (s, 1H, CH) 7.17-7.23, 7.32-7.34, 7.68, 7.69 (3m, 10H, Ph protons) 8.82 (br s, 1H, NH)	30.94 ($3CH_3$ of CMe_3), 41.90 (CMe_3) 52.84 (^{13}CH-CO_2Me, 52.51, 52.84 (CO_2Me) 82.94 (=^{13}C-COPh), 114.05 (=^{13}C-CO_2Me) 128.66, 128.74, 129.55, 129.82, 130.31, 132.86, 137.529 (2Ph carbons) 151.76 (=^{13}C-Ph), 161.50 (=^{13}C-NH) 170.11, 173.45 (2C = O of CO_2Me), 196.38 (C = O)	449 (M^+), 417 (M^+-OCH_3) 390 (M^+ - CO_2CH_3) 334 (M^+ - CO_2CH_3, *t*-Bu) 105 $(PhCO)^+$
5b	1.05, 1.16 (2t, 6H, $2CH_3$) 1.38 (s, 9H, *t*-Bu) 3.83-4.09 (2q, 4H, J = 6.601 Hz, $2CH_2$) 4.75 (s, 1H, CH) 7.09-7.33, 7.43-7.50, 7.61-7.2 (3m, 10H, 2Ph protons) 8.95 (br s, NH)	13.82, 14.55 ($2CH_3$ of Et), 30.50 ($3CH_3$ of CMe_3) 41.70 ($^{13}CMe_3$), 52.32 (^{13}CH-CO_2Et) 59.45, 60.97 ($2CH_2$ of CO_2Et), 83.93 (=^{13}C-CO_2Et) 113.62 (=^{13}C-COPh), 128.02, 128.31,128.60 105 $(PhCO)^+$ 128.78, 129.43, 130.00, 132.00, 133.18, 136.80 (Ph carbons) 151.09 (=^{13}C-Ph), 161.11 (=^{13}C-NH) 169.32, 172.55 (2C = O of CO_2Et), 196.81 (C = O)	477 (M^+) 404 (M^+ - CO_2Et) 348 (M^+ - CO_2Et, *t*-Bu)
5c	1.18 (s, 9H, CMe_3) 1.44, 1.47 (2S, 18H, $2CO_2$-*t*-Bu) 4.74 (s, 1H, CH) 7.11-7.75, 7.64-7.78 (2m, 10H, Ph protons) 8.97 (br s, NH)	28.44, 29.25 (2s, CH_3 of $2CO_2$*t*-Bu) 31.21 (s, CH_3 of N-*t*-Bu), 43.80 (^{13}C-NMe_3) 52.70 (^{13}CH-CO_2*t*-Bu), 79.83, 81.60 (2 ^{13}C $(CH_3)_3$ 83.96 (=^{13}C-CO_2*t*-Bu), 114.45 (=^{13}C-COPh) 128.62, 128.75, 129.30, 131.12, 133.37, 137.43 (2Ph carbons) 169.80, 172.15 (2C = O of CO_2*t*-Bu), 196.59 (C = O)	533 (M^+) 432 (M^+ - CO_2*t*-Bu) 376 (M^+ - CO_2*t*-Bu, *t*-Bu) 320 (M^+ - CO_2*t*-Bu, 2*t*-Bu) 105 $(PhCO)^+$
5d	1.25-1.89 (m, 10H, CH_2 of cyclohexyl) 2.64 (m, 1H, CH of cyclohexyl) 3.56, 3.72 (2s, 6H, $2CH_3O$) 4.73 (s, 1H, CH) 7.16-7.24, 7.31-7.36, 7.69-7.70 (3m, 10H, 2Ph protons) 8.33 (d, 1H, J = 8.062 Hz, NH)	23.40, 24.48, 28.69, 32.64 (CH_2 of cyclohexyl) 41.89 (CH of cyclohexyl) 50.48, 51.34 ($2CH_3$ of CO_2Me) 52.05 (^{13}CH-CO_2Me), 79.98 (=^{13}C-CO_2Me) 113.26 (=^{13}C-COPh) 128.72, 129.75, 129.93, 131.96, 132.32, 133.68, 135.83 (2Ph carbons), 151.49 (=^{13}C-Ph), 158.84 (=^{13}C-NH) 169.96, 173.64 (2C=O of CO_2Me), 196.80 (C=O)	475 (M^+) 416 (M^+ - CO_2Me) 334 (M^+ - CO_2Me, cyclohexyl) 302 (M^+ - CO_2Me, OMe, cyclohexyl) 105 $(PhCO)^+$
5e	1.05-1.23 (2t, 6H, CH_3 of Et) 1.34-1.56 (m, 10H, CH_2 of cyclohexyl) 2.64 (m, 1H, CH of cyclohexyl) 3.85-4.44 (2q, 4H, J-6.598 Hz, $CH_2$of Et) 4.68 (s, 1H, CH) 7.11-7.23, 7.38-7.46, 7.50-7.73 (3m, 10H, Ph protons) 8.64 (d, 1H, J = 8.045Hz, NH)	14.27, 14.38 ($2CH_3$ of Et) 24.75, 25.35, 29.61, 34.00 (CH_2 of cyclohexyl) 42.18 (CH of cyclohexyl), 50.33 (^{13}CH-CO_2Et) 59.61, 61.25 ($2CH_2$ of Et), 82.50 (=^{13}C-CO_2Et) 113.59 (=^{13}C-COPh) 127.55, 128.50, 128.98, 129.04, 130.31 132.81, 133.14, 133.74, 136.01, 137.01 (2Ph carbons), 152.301 (=^{13}C-Ph) 160.05 (=^{13}C-NH), 169.50, 173.05 (2C=O of CO_2Et) 196.93 (C=O)	503 (M^+), 430 (M^+ - CO_2Et) 347 (M^+ - CO_2Et, cyclohexyl) 105 $(PhCO)^+$
5f	1.32, 1.58 (2s, 18H, *t*-Bu protons) 1.20-1.78 (m, 10H, CH_2 of cyclohexyl) 2.71 (m, 1H, CH of cyclohexyl) 4.63 (s, 1H, CH) 7.20-7.35, 7.54-7.60, 7.70-7.82 (3m, 10H, Ph protons) 8.80 (d, 1H, J = 8.641 Hz, NH)	24.513, 26.78 (CH_3O of 2t-Bu) 23.66, 23.77, 27.58, 32.88 (CH_2 of cyclohexyl) 42.1 (CH of cyclohexyl), 49.11 (^{13}CH-CO_2t-Bu) 78.02, 79.89 ($2^{13}C$ $(CH_3)_3$) 113.405 (=^{13}C-COPh) 126.16, 126.99, 127.00, 127.32, 127.69, 128.56, 128.64, 131.42, 131.68, 135.77 (2Ph carbons) 149.72 (=^{13}C-Ph), 159.40 (=^{13}C-NH) 168.02, 170.70 (2C=O of CO_2t-Bu) 195.79 (C=O)	559 (M^+) 458 (M^+ - CO_2t-Bu) 377 (M^+ - CO_2t-Bu, cyclohexyl) 105 $(PhCO)^+$

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