# Three-Component Reaction of an Isocyanide and a Dialkyl Acetylenedicarboxylate with a Phenacyl Halide in the Presence of Water: An Efficient Method for the One-Pot Synthesis of γ-Iminolactone Derivatives

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The zwitterion, formed from the reaction of an alkyl isocyanide and a dialkyl acetylenedicarboxylate, reacts with phenacyl halides in $H_2O$ to produce γ-iminolactone derivatives in high yields. $H_2O$ helps to avoid the use of highly toxic and environmentally unfavorable solvents for this conversion.

**Introduction.** – Many protocols for the synthesis of iminolactones have been reported [1–8]. The most widely used approach are isocyanide-based reactions [1–5]. As early as 1982, *Saegusa* and his co-workers reported on the $Et_2AlCl$-mediated reaction of α,β-unsaturated carbonyl compounds with MeNC, leading to unsaturated *N*-substituted iminolactones, which can be easily converted to γ-butyrolactone [1]. Recently, *Chatani et al.* re-examined a catalytic [1+4] cycloaddition reaction of isocyanides and α,β-unsaturated CO compounds in the presence of a catalytic amount of $GaCl_3$, leading to unsaturated iminolactone derivatives [4]. Moreover, $GaCl_3$ catalyzed the double insertion of aryl isocyanides into terminal and disubstituted epoxides, which led finally to α,β-unsaturated α-amino iminolactones [5]. Also, the $Pd(Ph_3P)_4$-catalyzed reaction of 4,4-disubstituted allenecarboxamides and organic iodides in the presence of $K_2CO_3$ in toluene afforded iminolactones [6]. Finally, the haloiminolactonization of 4,4-disubstituted allenecarboxamides with $CuX_2$ (X=Cl, Br) or $I_2$ in THF also provided unsaturated iminolactones [7].

Here, we report a simple and practical procedure to prepare highly functionalized γ-iminolactones by a one-pot three-component reaction of isocyanides, acetylenedicarboxylates, and phenacyl chloride or bromide in the presence of $H_2O$ (*Scheme 1*).

**Results and Discussion.** – As part of our ongoing program on the development of efficient and robust methods for the preparation of heterocyclic compounds [9–15], we describe here a clean and efficient process in $H_2O$ at room temperature leading to γ-iminolactone derivatives **4** (*Scheme 1* and *Table*). We also used acetophenone, 1-benzyl- and 1-(pyridin-2-yl)ethanone instead of phenacyl halides in this reaction, but the yields of the corresponding products were low and several by-products were obtained.

As indicated in the *Table*, the 1:1:1 addition reaction of phenacyl halides with dimethyl acetylenedicarboxylate and *t*-BuNC occured in $H_2O$ and $CH_2Cl_2$ at room temperature to produce dimethyl 5-(*tert*-butylimino)-2-(chloromethyl)-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate (**4a**). In the presence of $H_2O$, the yield of **4a** (97%) was

Scheme 1. *Three-Component Synthesis of γ-Iminolactone Derivatives* **4** *in* $H_2O$ (see the *Table*)

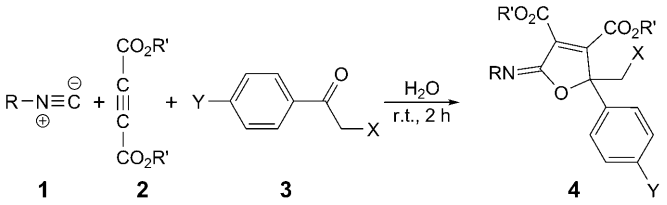



Table. *$H_2O$-Promoted Synthesis of γ-Iminolactone Derivatives* **4** (*cf. Scheme 1*)

| | R′ | R | X | Y | Yield [%][a]) | Yield [%][b]) |
|---|---|---|---|---|---|---|
| **4a** | Me | *t*-Bu | Cl | H | 77 | 97 |
| **4b** | Me | Cyclohexyl | Cl | H | 74 | 92 |
| **4c** | Me | 1,1,3,3-Tetramethylbutyl | Cl | H | 71 | 88 |
| **4d** | Et | *t*-Bu | Cl | H | 74 | 94 |
| **4e** | Et | Cyclohexyl | Cl | H | 70 | 90 |
| **4f** | Et | 1,1,3,3-Tetramethylbutyl | Cl | H | 69 | 84 |
| **4g** | Me | *t*-Bu | Br | Br | 90[c]) | 97 |
| **4h** | Me | Cyclohexyl | Br | Br | 97[c]) | 97 |
| **4i** | Et | *t*-Bu | Br | Br | 80[c]) | 90 |
| **4j** | Et | Cyclohexyl | Br | Br | 83[c]) | 92 |

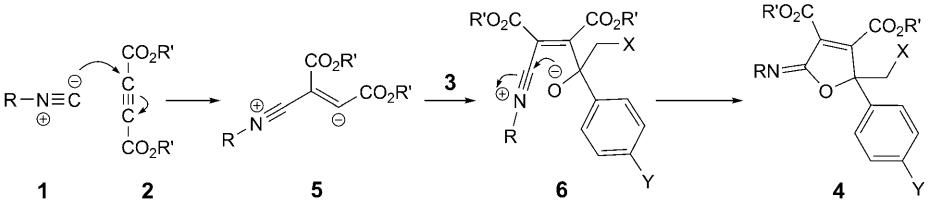
[a]) Yields of isolated **4**; reaction conditions: $CH_2Cl_2$, r.t., 12 h. [b]) Yields of isolated **4**; reaction conditions: $H_2O$, r.t., 2 h. [c]) Synthesis of compounds **4g**–**4j** in $CH_2Cl_2$ was reported in [8b].

higher than in $CH_2Cl_2$ as solvent (77%), and also the time of product formation was shorter (2 h) in $H_2O$ than in $CH_2Cl_2$ (12 h). The structures of the products were deduced from their IR, $^1$H- and $^{13}$C-NMR, and mass spectra. The mass spectra of **4** displayed molecular-ion peaks at the appropriate *m*/*z* values. The $^1$H-NMR spectrum ($CDCl_3$) of **4a** consisted of a *singlet* at 1.38 ppm ($Me_3C$), two further *singlet*s at 3.78 and 3.90 ppm (COOMe), an *AB* system at 4.20 and 4.64 ppm with $J_{AB} = 11.8$ Hz ($CH_2Cl$), and a *multiplet* at 7.26–7.40 ppm for the aromatic H-atoms. The $^1$H-decoupled $^{13}$C-NMR spectrum of **4a** showed 15 distinct resonances; partial assignment of these resonances is given in the *Exper. Part*. The $^1$H- and $^{13}$C-NMR spectra of compounds **4b**–**4j** were similar to those of **4a**, except for the aromatic moiety and the alkyl groups, which exhibited characteristic signals with appropriate chemical shifts.

Although we have not established experimentally the mechanism of the reaction, a plausible reaction sequence that accounts for the formation of **4** is depicted in *Scheme 2*. It is conceivable that the initial step is the formation of zwitterionic intermediate **5** from isocyanide **1** and acetylenedicarboxylate **2**, which then adds to the electron-poor CO group of phenacyl halides **3**, leading to a dipolar specie **6**. Cyclization of **6** leads then to the γ-iminolactone **4**.

**Conclusions.** – In summary, we have established $H_2O$ as a novel reaction medium for the synthesis of highly functionalized γ-iminolactone derivatives. This procedure

Scheme 2. *Proposed Mechanism for the Formation of γ-Iminolactone Derivatives* **4**




offers significant advantages such as operational simplicity, mild reaction conditions, enhanced rates, ease of isolation of products, cleaner reaction profiles, and $H_2O$ as solvent, which makes it a useful and an attractive alternative for the synthesis of γ-iminolactone derivatives.

## Experimental Part

*General.* Freshly distilled solvents were used throughout, and anh. solvents were dried according to the procedure of *Perrin* and *Armarego* [16]. IR Spectra (KBr): *Mattson-1000* FT-IR spectrophotometer. $^1$H- and $^{13}$C-NMR spectra: *Bruker 250* spectrometer in $CDCl_3$ with TMS as internal standard. MS: *FINNIGAN-MAT 8430* mass spectrometer operating at an ionization potential of 20 eV. Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

*General Procedure.* To a magnetically stirred soln. of 2-chloroacetophenone (1 mmol) and dimethyl acetylenedicarboxylate (1 mmol) in $H_2O$ (3 ml) was added dropwise of a soln. of *t*-BuNC (1 mmol) in $H_2O$ (1 ml) at r.t. over 5 min. The mixture was stirred for 2 h. The solvent was removed under reduced pressure, and the viscous residue was purified by flash column chromatography (CC; $SiO_2$; petroleum ether/AcOEt). The solvent was removed under reduced pressure, and product **4a** was obtained as colorless oil (for yields, see the *Table*).

*Dimethyl 5-(*tert*-Butylimino)-2-(chloromethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate* (**4a**). IR: 2937, 2870, 1748, 1715, 1680, 1452, 1244. $^1$H-NMR: 1.38 (*s*, *t*-Bu); 3.78, 3.90 (2*s*, 2 MeO); 4.20, 4.64 (*AB*, $J = 11.8$, $CH_2Cl$); 7.26–7.40 (*m*, 5 arom. H). $^{13}$C-NMR: 29.54 ($Me_3C$); 48.08 ($CH_2Cl$); 52.84, 52.95 (2 MeO); 54.96 ($Me_3C$); 91.35 (C(2)); 125.75, 128.82, 129.07 (5 arom. CH); 136.73, 139.04, 141.20 (3 C); 152.31 (C=N); 161.13, 162.37 (2 C=O). EI-MS: 380 (6), 356 (100), 302 (83), 250 (38), 236 (41), 157 (9), 105 (23), 57 (23), 41 (15). Anal. calc. for $C_{19}H_{22}ClNO_5$: C 60.08, H 5.84, N 3.69; found: C 60.00, H 5.78, N 3.58.

*Dimethyl 2-(Chloromethyl)-5-(cyclohexylimino)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate* (**4b**). IR: 2940, 2857, 1751, 1720, 1686, 1473, 1254. $^1$H-NMR: 1.15–1.90 (*m*, 5 $CH_2$ of cyclohexyl); 3.69–3.76 (*m*, CH–N); 3.77, 3.90 (2*s*, 2 MeO); 4.20, 4.64 (*AB*, $J = 11.8$, $CH_2Cl$); 7.26–7.40 (*m*, 5 arom. H). $^{13}$C-NMR: 24.82 (2 $CH_2(\beta)$ of cyclohexyl); 25.72 (1 $CH_2(\gamma)$ of cyclohexyl); 33.47 (2 $CH_2(\alpha)$ of cyclohexyl); 47.98 ($CH_2Cl$); 52.87, 53.04 (2 MeO); 56.83 (CH–N); 90.62 (C(2)); 125.67, 128.88, 129.18 (5 arom. CH); 136.61, 137.69, 142.30 (3 C); 154.36 (C=N); 161.12, 162.13 (2 C=O). EI-MS: 406 (25), 398 (30), 378 (48), 352 (36), 332 (100), 290 (60), 250 (33), 105 (50), 98 (12), 55 (33), 41 (19). Anal. calc. for $C_{21}H_{24}ClNO_5$: C 62.14, H 5.96, N 3.45; found: C 62.09, H 5.88, N 3.39.

*Dimethyl 2-(Chloromethyl)-2,5-dihydro-2-phenyl-5-[(1,1,3,3-tetramethylbutyl)imino]furan-3,4-dicarboxylate* (**4c**). IR: 2960, 2878, 1751, 1720, 1680, 1474, 1246. $^1$H-NMR: 1.00 (*s*, $Me_3C$); 1.42 (*s*, $Me_2CN$); 1.66 (*s*, $CH_2CMe_3$); 3.76, 3.86 (2*s*, 2 MeO); 4.20, 4.61 (*AB*, $J = 11.8$, $CH_2Cl$); 7.36–7.44 (*m*, 5 arom. H). $^{13}$C-NMR: 29.68 ($Me_2C$); 31.63 ($Me_3C$); 31.94 ($Me_3C$); 52.76, 52.80 (2 MeO); 55.32 ($CH_2CMe_3$); 56.50 ($Me_2C$); 91.44 (C(2)); 125.81, 128.77, 129.03 (5 arom. CH); 137.32, 139.59, 140.42 (3 C); 150.99 (C=N); 161.19, 162.45 (2 C=O). EI-MS: 436 (30), 394 (100), 362 (30), 282 (28), 250 (90), 233 (35), 91 (5), 57 (30), 41 (10). Anal. calc. for $C_{23}H_{30}ClNO_5$: C 63.37, H 6.94, N 3.21; found: C 63.28, H 6.88, N 3.18.

*Diethyl 5-(*tert*-Butylimino)-2-(chloromethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate* (**4d**). IR: 2938, 2876, 1743, 1722, 1680, 1448, 1243. $^1$H-NMR: 1.24, 1.35 (2*t*, *J* = 7.3, 2 *Me*CH$_2$); 1.37 (*s*, *t*-Bu); 4.36, 4.20 (2*q*, *J* = 7.3, 2 MeC*H*$_2$); 4.21, 4.61 (*AB*, *J* = 11.8, CH$_2$Cl); 7.26–7.40 (*m*, 5 arom. H). $^{13}$C-NMR: 13.74, 14.06 (2 *Me*CH$_2$); 29.55 (*Me*$_3$C); 48.15 (CH$_2$Cl); 54.89 (Me$_3$*C*); 62.00, 62.09 (2 Me*C*H$_2$); 91.33 (C(2)); 125.83, 128.74, 128.98 (5 arom. CH); 136.85, 138.94, 141.06 (3 C); 152.51 (C=N); 160.76, 162.00 (2 C=O). EI-MS: 408 (12), 380 (5), 352 (100), 306 (95), 250 (50), 233 (39), 156 (15), 105 (20), 57 (25), 41 (13). Anal. calc. for $C_{21}H_{26}ClNO_5$: C 61.84, H 6.42, N 3.69; found: C 61.30, H 5.78, N 3.58.

*Data of Diethyl 2-(Chloromethyl)-5-(cyclohexylimino)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate* (**4e**). IR: 2944, 2857, 1751, 1718 1685, 1435, 1258. $^1$H-NMR: 1.24, 1.35 (2*t*, *J* = 7.3, 2 *Me*CH$_2$); 1.21–1.89 (*m*, 5 CH$_2$ of cyclohexyl); 3.69–3.74 (*m*, CH–N); 4.20, 4.62 (*AB*, $J_{AB}$ = 11.8, CH$_2$Cl); 4.21, 4.33 (2*q*, *J* = 7.3, 2 MeC*H*$_2$); 7.26–7.42 (*m*, 5 arom. H). $^{13}$C-NMR: 13.76, 14.04 (2 *Me*CH$_2$); 24.75 (2 CH$_2$($\beta$) of cyclohexyl); 25.76 (CH$_2$($\gamma$) of cyclohexyl); 33.46 (2 CH$_2$($\alpha$) of cyclohexyl); 48.05 (CH$_2$Cl); 56.66 (CH–N); 62.03, 62.18 (2 Me*C*H$_2$); 90.61 (C(2)); 125.76, 128.81, 129.09 (5 arom. CH); 136.77, 137.56, 142.13 (3 C); 154.47 (C=N); 160.76, 161.71 (2 C=O). EI-MS: 434 (10), 408 (25), 395 (30), 378 (48), 352 (36), 332 (100), 290 (60), 250 (33), 233 (35), 98 (12), 105 (50), 55 (33), 41 (19). Anal. calc. for $C_{23}H_{28}ClNO_5$: C 63.66, H 6.50 N 3.23; found: C 63.09, H 5.88, N 3.39.

*Diethyl 2-(Chloromethyl)-2-phenyl-5-[(1,1,3,3-tetramethylbutyl)imino]-2,5-dihydrofuran-3,4-dicarboxylate* (**4f**). IR: 2967, 2878, 1746, 1715, 1685, 1457, 1222. $^1$H-NMR: 1.00 (*s*, Me$_3$C); 1.27, 1.36 (2*t*, *J* = 7.3, 2 *Me*CH$_2$); 1.42 (*s*, Me$_2$C); 1.66 (*s*, C*H*$_2$CMe$_3$); 4.20, 4.59 (*AB*, $J_{AB}$ = 11.8, CH$_2$Cl); 4.22, 4.33 (2*q*, *J* = 7.3, 2 MeC*H*$_2$); 7.26–7.49 (*m*, 5 arom. H). $^{13}$C-NMR: 13.74, 14.08 (2 *Me*CH$_2$); 29.75 (*Me*$_2$CN); 31.68 (*Me*$_3$C); 31.93 (Me$_3$*C*); 48.18 (CH$_2$Cl); 55.27 (*CH*$_2$CMe$_3$); 58.41 (Me$_2$*C*N); 61.96, 62.03 (2 Me*C*H$_2$); 91.39 (C(2)); 125.90, 128.70, 128.93 (5 arom. CH); 137.11, 139.62, 140.95 (3 C); 153.86 (C=N); 160.84, 162.10 (2 C=O). EI-MS: 464 (13), 428 (38), 408 (100), 392 (90), 362 (36), 296 (32), 250 (80), 233 (40), 105 (37), 57 (45), 41 (20). Anal. calc. for $C_{25}H_{34}ClNO_5$: C 64.71, H 7.39, N 3.02; found: C 64.09, H 7.22, N 2.99.

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