Multicomponent Transformation of Isoindoline-1,3-diimine (=1*H*-Isoindole-1,3(2*H*)-diimine), Acetylenic Esters, and Triphenylphosphine to Novel Dihydropyrimido[2,1-*a*]isoindole Derivatives

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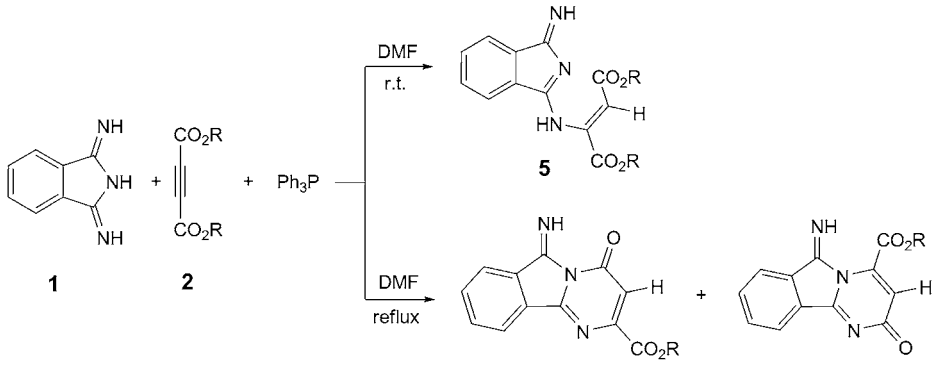
The three-component reaction of the zwitterions generated from dialkyl acetylenedicarboxylates (=dialkyl but-2-ynedioates and triphenylphosphine (Ph_3P) with isoindoline-1,3-diimine (=1*H*-isoindole-1,3(2*H*)-diimine) is described (*Scheme 1*). This reaction affords the corresponding special type of substituted dihydropyrimido[2,1-*a*]isoindole derivatives in good yields without using any catalyst and activation (*Table*).

Introduction. – In recent years, the construction of the hydropyrimidine frameworks has been the subject of numerous investigations [1], since six-membered pyrimidine and fused pyrimidine heterocycles are ubiquitous structural components of several natural products with a wide range of biological activities [2–5]. Among them, pyrimidoindoles and pyrimidoisoindoles are well known for their potential biological and pharmacological activities, especially antitumor [6], cytotoxic [7], and anti-HIV [8] activities. Due to the biological activity of fused pyrimidines and the little attention paid to the synthesis of pyrimidoisoindole derivatives [9][10], we wish herein to report, in continuation of our recent investigations [11–15], a simple and efficient method for the preparation of novel dihydropyrimido[2,1-*a*]isoindole derivatives.

Results and Discussion. – The reaction of isoindoline-1,3-diimine (=1*H*-isoindole-1,3(2*H*)-diimine; **1**) and dialkyl acetylenedicarboxylates (=dialkyl but-2-ynedioates) **2** in the presence of Ph_3P in refluxing *N*,*N*-dimethylformamide (DMF) leads within 24 h to a mixture of dihydropyrimido[2,1-*a*]isoindole derivatives **3a**/**4a** (or **3b**/**4b**) in different ratios. Unfortunately, the separation of these mixture by chromatography was unsuccessful. When we used the di(*tert*-butyl) ester **2c**, only **3c** was obtained as the sole product in high yield. *N*-Vinyl-substituted isoindolinediimine derivatives **5** were only isolated as by-product of these reactions (*Scheme 1*).

We first investigated the reactions of **1** and **2a** in the presence of Ph_3P under different conditions (*Table*). In solvents such as dioxane, MeCN, CH_2Cl_2, and THF at room temperature, the conversion of **1** was low due to the low solubility in these solvents. When DMF was used as solvent, the conversion of **1** was excellent, and the *N*-vinyl-substituted isoindolinediimine derivative **5a** was obtained as major product in high yield. Next, we examined the thermal reaction of **1** with **2a** and Ph_3P in different solvents (*Table*). The best results were obtained in refluxing DMF. When the thermal

Scheme 1. *Reaction of Isoindoline-1,3-diimine* (**1**) *and Dialkyl Acetylenedicarboxylates* **2** *in the Presence of Ph_3P in DMF*



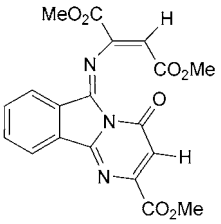
	R	Yield [%] at reflux		Yield [%] at r.t.	
		3/4	**5**	**3/4**	**5**
a	Me	88	5	–	94
b	Et	84	8	–	92
c	*t*-Bu	80	12	–	90

Table. *Reaction of Isoindoline-1,3-diimine* (**1**), *Acetylenic Ester* (**2a**), *and Ph_3P under Different Conditions for 24 h*

Solvent	Reaction condition	Yield [%] of products	
		3a/4a	**5a**
Dioxane	r.t.	–	10
MeCN	r.t.	–	14
CH_2Cl_2	r.t.	–	–
THF	r.t.	–	6
DMF	r.t.	–	94
Dioxane	reflux	25	–
MeCN	reflux	12	–
CH_2Cl_2	reflux	–	–
THF	reflux	15	–
DMF	reflux	88	5

reaction was performed in refluxing dioxane, only product **3a** was isolated in a pure state as the sole product, but the yield of the product was much lower. So we performed all of the reactions in refluxing DMF. In the reaction of **1** with **2a** and Ph_3P in refluxing DMF, dihydropyrimido-isoindole **6a** (*Fig.*) was also isolated as by-product in 3% yield.

The structures of compounds **3a**–**3c**, **4a**, and **4b** were deduced from their IR, mass, and high-field ^{1}H- and ^{13}C-NMR spectra. Although, we were not able to separate the products **3a**/**4a** or **3b**/**4b** in pure form, the NMR data for each isomer could be extracted from the spectrum of the mixture. The ^{1}H- and ^{13}C-NMR spectra indicated for **3a**/**4a** a



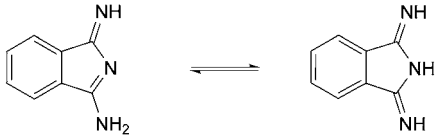
6a Figure. *Dihydropyrimido-isoindole by-product* **6a**

ratio of 3:1, which was determined by integration of the well-resolved δ(H) of the olefinic H-atoms.

The ^{1}H-NMR spectrum of **3a** exhibited two *s* at δ(H) 3.92 for MeO of the carboxylate at C(2) and at δ(H) 7.09 for H–C(3). A further *s* was observed for the imino group at C(6) (δ(H) 11.18), along with characteristic *m* for the aromatic H-atoms. The H-decoupled ^{13}C-NMR spectrum of **3a** showed the expected 13 distinct resonances. The ^{1}H-NMR and ^{13}C-NMR data of **4a** were similar to those of **3a**, however, present with lower intensity (ratio **3a**/**4a** 3:1).

Isoindoline-1,3-diimine (**1**) is an NH-acid with three acidic H-atoms, which are involved in a tautomer equilibrium in solution [16] (*Scheme 2*).

Scheme 2. *Tautomer Equilibrium of Isoindoline-1,3-diimine* (**1**)



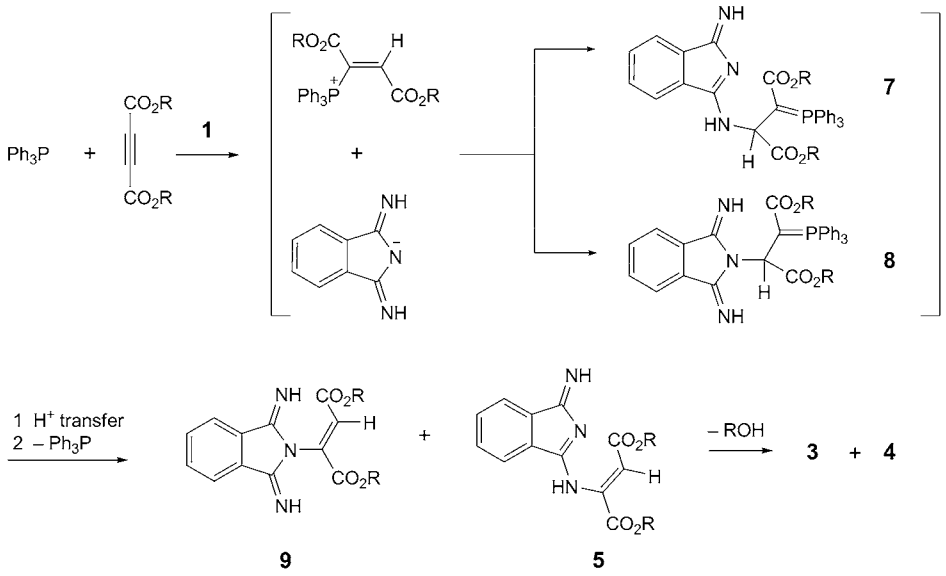
After initial addition of Ph_3P to the acetylenic ester **2** and the subsequent protonation of the reactive 1:1 adduct by the NH-acid **1**, electrophilic attack of the vinyltriphenylphosphonium cation on the anion of **1** forms the phosphoranes **7** and **8**, which *via* H-atom transfer and removal of Ph_3P (which is recycled) lead to the *N*-vinyl-substituted isoindolinediimine derivatives **5** and **9** (*Scheme 3*). The final products **3** and **4** are then presumably produced by an intramolecular lactamization.

Conclusions. – In summary, the reaction described herein represents a simple entry into the synthesis of polyfunctional dihydropyrimido[2,1-*a*]isoindole derivatives of potential pharmaceutical interest. The present method has the advantage of being performed under neutral conditions requiring no activation or modification of the substrates, of a short reaction time of moderate yields, and of a simple workup procedure. Further investigations of the present method will be required to establish its utility and scope.

Experimental Part

General. Dialkyl but-2-ynedioates **2**, Ph_3P, and isoindoline-1,3-diimine (**1**) were obtained from *Fluka* (Buchs, Switzerland) and were used without further purification. Column chromatography (CC): silica

Scheme 3. *Mechanism of the Reaction of Isoindoline-1,3-diimine* (**1**) *and Dialkyl Acetylenedicarboxylates* **2** *in the Presence of* Ph_3P



gel (SiO_2, 230–400 mesh; *Merck*). M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *FT-IR-Bruker-VECTOR-22* spectrometer; in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX-400-Avance* instrument; at 400 (^{1}H) and 100 MHz (^{13}C), in (D_6)DMSO or $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan-Matt-8430* mass spectrometer; at 70 eV; in *m*/*z*.

*Dihydropyrimido[2,1-*a*]isoindole Derivatives* **3**, **4**, *and* **6a**: *General Procedure.* To a stirred soln. of Ph_3P (0.52 g, 2 mmol) and isoindoline-1,3-diimine (**1**; 0.29 g, 2 mmol) in DMF (10 ml) at –5° was added dropwise over 10 min a soln. of dialkyl but-2-ynedioate (0.28 g, 2 mmol) in DMF (2 ml). The mixture was then heated under reflux for 24 h. The solvent was evaporated and the residue separated by CC (hexane/AcOEt).

*Methyl 4,6-Dihydro-6-imino-4-oxopyrimido[2,1-*a*]isoindole-2-carboxylate* (**3a**) *and Methyl 2,6-Dihydro-6-imino-2-oxopyrimido[2,1-*a*]isoindole-4-carboxylate* (**4a**): Yield 0.44g (88%). White powder. IR: 1720 (C=O), 1747 (C=O), 3265–3275 (NH). ^{1}H-NMR (**3a**): 3.92 (*s*, MeO); 7.09 (*s*, H–C(3)); 7.53–8.12 (*m*, 4 arom. H); 11.18 (*s*, NH). ^{1}H-NMR (**4a**): 3.88 (*s*, MeO); 7.03 (*s*, H–C(3)); 7.53–8.03 (*m*, 4 arom. H); 13.48 (*s*, NH). ^{13}C-NMR (**3a**): 53.6 (MeO); 118.9 (C(3)); 123.5, 123.7, 131.9, 132.0 (4 arom. CH); 134.3, 134.5 (2 arom. C); 151.2, 154.4, 155.9 (2 C=N, C–N); 162.3, 164.2 (2 C=O). ^{13}C-NMR (**4a**): 53.4 (MeO); 111.4 (C(3)); 129.2, 129.3, 132.51, 132.53 (4 arom. CH); 133.6, 134.7 (2 arom. C); 150.5, 154.4, 156.1 (2 C=N, C–N); 162.3, 164.8 (2 C=O). MS: 255.23 (100, M^+), 169 (32), 129 (35).

*Ethyl 4,6-Dihydro-6-imino-4-oxopyrimido[2,1-*a*]isoindole-2-carboxylate* (**3b**) *and Ethyl 2,6-Dihydro-6-imino-2-oxopyrimido[2,1-*a*]isoindole-4-carboxylate* (**4b**): Yield 0.45g (84%). White powder. IR: 1715 (C=O), 1743 (C=O), 3180–3200 (NH). ^{1}H-NMR (**3b**): 1.35 (*t*, $J = 7.2$, Me); 4.37 (*q*, $J = 7.2$, CH_2O); 7.07 (*s*, H–C(3)); 7.83–8.09 (*m*, 4 arom. H); 11.17 (*s*, NH). ^{1}H-NMR (**4b**): 1.31 (*t*, $J = 7.2$, Me); 4.33 (*q*, $J = 7.2$, CH_2O); 7.03 (*s*, H–C(3)); 7.75–8.05 (*m*, 4 arom. H); 13.44 (*s*, NH). ^{13}C-NMR (**3b**): 14.4 (Me); 62.6 (CH_2O); 118.8 (C(3)); 123.5, 123.7, 130.6, 133.6 (4 arom. CH); 134.2, 134.5 (2 arom. C); 151.4, 154.3, 155.8 (2 C=N, C–N); 162.25, 163.6 (2 C=O). ^{13}C-NMR (**4b**): 14.4 (Me), 62.3 (CH_2O); 111.7 (C(3)); 132.0, 132.1, 133.1, 133.6 (4 arom. CH); 134.2, 134.7 (2 arom. C); 151.4, 154.3, 155.9 (2 C=N, C–N); 162.3, 164.0 (2 C=O). MS: 269.26 (21, M^+), 198 (100), 130 (85), 102 (50).

tert-*Butyl 4,6-Dihydro-6-imino-4-oxopyrimido[2,1-*a*]isoindole-2-carboxylate* (**3c**): Yield 0.50g (80%).White powder. M.p. 116–117°. IR: 1720 (C=O), 1742 (C=O), 3195–3215 (NH). ^{1}H-NMR: 1.63 (*s*, Me_3CO); 7.15 (*s*, H–C(3)); 7.73–8.21 (*m*, 4 arom. H); 11.39 (*s*, NH). ^{13}C-NMR: 27.9 (Me_3CO); 83.8 (Me_3CO); 118.3 (C(3)); 123.6, 123.7, 131.6, 132.9 (4 arom. CH); 133.5, 134.0 (2 arom. C); 152.4, 153.8, 155.4 (2 C=N, C–N); 162.1, 162.3 (2 C=O).

*Dimethyl (2Z)-2-{[(6Z)-2-(Methoxycarbonyl)-4-oxopyrimido[2,1-*a*]isoindol-6(4*H*)-ylidene]amino}but-2-enedioate* (**6a**): Yield 0.23g (3%). White powder. M.p. 178–179°. IR: 1726 (C=O). ^{1}H-NMR: 3.51, 3.80, 3.91 (3 *s*, 3 MeO); 6.10, 7.00 (2 *s*, H–C(3), H–C(3′)); 7.53–7.92 (*m*, 4 arom. H). ^{13}C-NMR: 52.01, 53.60, 53.88 (3 MeO); 105.26, 119.14 (C(3), C(3′)); 123.80, 125.51, 129.17, 129.29 (4 arom. CH); 134.88, 134.96 (2 arom. C); 146.59 (C(4′)); 150.26, 156.69, 158.27 (2 C=N, C–N); 162.55, 184.01, 165.06 (3 C=O).

*Dialky (2Z)-(2-[1-Imino-1*H*-isoindol-3-yl)amino]but-2-enedioates* **5a**–**5c**: *General Procedure.* To a stirred soln. of Ph_3P (0.52 g, 2 mmol) and **1** (0.29 g, 2 mmol) in DMF (10 ml) at –5° was added dropwise a soln. of dialkyl but-2-enedioate (0.28 g, 2 mmol) in DMF (2 ml) over 10 min. The mixture was then stired for 24 h at r.t. The solvent was evaporated and the residue separated by CC (hexane/AcOEt).

*Dimethyl (2Z)-2-[(1-Imino-1*H*-isoindol-3-yl)amino]But-2-enedioate* (**5a**): Yield 0.54g (94%).Yellow powder. M.p. 165–166°. IR: 1726 (C=O), 3430 (NH). ^{1}H-NMR: 3.63, 3.74 (2 *s*, 2 MeO); 5.85 (*s*, H–C(3)); 7.57–7.92 (*m*, 4 arom. H); 9.09, 9.18 (2 *s*, 2 NH). ^{13}C-NMR: 51.7, 52.5 (2 MeO); 109.4 (C=CH); 121.9, 122.3, 131.4, 132.1 (4 arom. CH); 135.4, 139.9 (2 arom. C); 155.2 (*C*=*C*H); 166.3, 167.0 (2 C=N); 169.9, 172.8 (2 C=O). MS: 287.27 (55, M^+), 256 (92), 228 (33), 197 (91), 129 (100), 102 (69).

*Diethyl (2Z)-2-[(1-Imino-1*H*-isoindol-3-yl)amino]but-2-enedioate* (**5b**): Yield 0.58g (92%). Yellow powder. M.p. 134–135°. IR: 1731 (C=O), 3339 (NH). ^{1}H-NMR: 1.33, 1.37 (2 *t*, J = 7.2, 2 Me); 4.28, 4.35 (2 *q*, J = 7.2, 2 CH_2O); 5.65 (*s*, H–C(3)); 7.56–7.92 (*m*, 4 arom. H); 9.11 (2 br. *s*, 2 NH). ^{13}C-NMR: 14.0, 14.2 (2 Me); 61.0, 62.1 (2 MeO); 108.7 (C=CH); 120.3, 122.9, 131.0, 131.9 (4 arom. CH); 134.4, 138.0 (2 arom. C); 154.1 (*C*=*C*H); 165.3, 167.2 (2 C=N); 169.9, 171.1 (2 C=O). MS: 315.32 (15, M^+), 169 (99), 147 (100), 129 (97), 103 (56), 76 (69).

*Di(*tert*-butyl) (2Z)-2-[(1-Imino-1*H*-isoindol-3-yl)amino]but-2-enedioate* (**5c**): Yield 0.66g (90%). Yellow powder. M.p. 167–168°. IR: 1715 (C=O), 3275 (NH). ^{1}H-NMR: 1.43, 1.45 (2 *s*, 2 Me_3CO); 5.61 (*s*, H–C(3)); 7.56–7.91 (*m*, 4 arom. H); 8.92, 9.02 (2 *s*, 2 NH). ^{13}C-NMR: 28.1, 28.33 (2 Me_3CO); 80.0, 81.5 (2 Me_3CO); 109.8 (C=CH); 121.7, 122.2, 131.2, 131.9 (4 arom. CH); 135.6, 140.0 (2 arom. C); 154.9 (*C*=*C*H); 165.2, 165.3 (2 C=N); 169.1, 172.7 (2 C=O). MS: 371.38 (9, M^+), 170 (100), 242 (25), 215 (46), 129 (56), 102 (24), 57 (71).

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