Efficient Synthesis of Tetrahydropyrimidines and Pyrrolidines by a Multicomponent Reaction of Dialkyl Acetylenedicarboxylates (= Dialkyl But-2-ynedioates), Amines, and Formaldehyde in the Presence of Iodine as a Catalyst[1])

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Iodine was explored as an efficient catalyst for the synthesis of tetrahydropyrimidines **4** and pyrrolidines **5** by a multicomponent reaction of dialkyl acetylenedicarboxylates (=dialkyl but-2-ynedioates) **1**, amines **2**, and HCHO **3** at room temperature (*Scheme*). When the molar ratios of these substrates were 1:2:4 and 1:1:4, tetrahydropyrimidines and pyrrolidines were formed, respectively. The products were obtained in high yields (73–85%) within a short period of time (25–35 min).

Introduction. – Tetrahydropyrimidines and pyrrolidines are important biologically active heterocycles. The compounds of the first group possess interesting muscarinic agonist activity [1], and anti-inflammatory [2] and antiviral properties [3]. Pyrrolidines, on the other hand, have been recognized as anticancer [4], antibacterial [5], and antifungal agents [6]. However, the compounds were prepared earlier only by a few methods involving the reactions of amines or nitro compounds, dialkyl acetylenedicarboxylates (=dialkyl but-2-ynedioates) and HCHO at high temperature or in the presence of acid catalysts [7–12]. Moreover, the pyrrolidines initially prepared by *Jiang* and co-workers [10] were originally characterized as oxazine derivatives whose structures have recently been revised [11]. Actually, there are only these two reports of a similar procedure for the preparation of pyrrolidines starting from amines following the stated method. Thus, the chemistry of tetrahydropyrimidines and pyrrolidines are interesting. Here, we report an alternative efficient mild method for the preparation of these heterocycles.

Results and Discussion. – In continuation of our work on the development of useful synthetic methodologies [13–17], we observed that tetrahydropyrimidines and pyrrolidines can conveniently be prepared by a three-component reaction of a dialkyl acetylenedicarboxylate, an amine, and HCHO in the presence of iodine at room temperature (*Scheme*). When the molar ratios of these substrates were 1:2:4 and 1:1:4, 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidines and 1,3,3-trisubstituted 4,5-dioxopyrrolidines respectively, were formed (*Scheme*).

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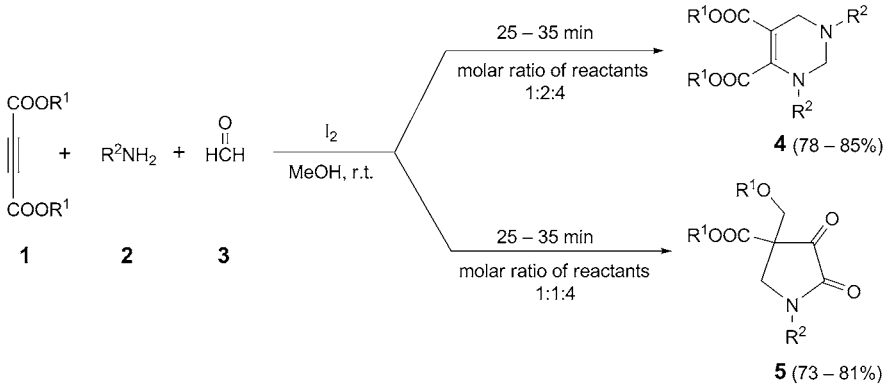
[1]) Part 224 in the series 'Studies on Novel Synthetic Methodologies'.

Scheme



Initially, the reaction of 4-bromoaniline with dimethyl acetylenedicarboxylate and HCHO (molar ratio 1:2:4) was carried out in the presence of different catalysts such as trifluoroborane ether (1:1) ($BF_3 \cdot Et_2O$), *p*-toluenesulfonic acid (TsOH), phosphomolybdic acid on silica gel ($PMA \cdot SiO_2$), 2,4,6-trichlorotriazine (TCT), $Ce(NH_4)_2(NO_3)_6$, iodine (I_2), and perchloric acid adsorbed on silica gel ($HClO_4 \cdot SiO_2$) (*Table 1*). Considering the yield (81%) of the corresponding tetrahydropyrimidine and the time of the conversion (35 min), I_2 was decided to be the best catalyst for the present conversion and was subsequently utilized to prepare a series of tetrahydropyrimidines from different amines (*Table 2*). Both dimethyl and diethyl acetylenedicarboxylate were used to prepare these compounds. The conversion was complete within 25–35 min, and the products were formed in high yields (78–85%).

Table 1. *Synthesis of Tetrahydropyrimidines* **4d** *in the Presence of Different Catalysts*[a])

Catalyst	Time	Yield [%][b])	Catalyst	Time	Yield [%][b])
$BF_3 \cdot Et_2O$	2 h	10	$HClO_4 \cdot SiO_2$	1 h	50
TsOH	1 h	trace	$Ce(NH_4)_2(NO_3)_6$	45 min	66
$PMA \cdot SiO_2$	1 h	20	I_2	35 min	81
TCT	5 h	10			

[a]) Reaction conditions: dimethyl acetylenedicarboxylate (1.0 mmol), 4-bromoaniline (2.0 mmol), HCHO (4.0 mmol), and catalyst (10 mol-%) at r.t. [b]) Yield of pure compound after CC.

A similar reaction was carried out with a molar ratio 1:1:4 of dialkyl acetylenedicarboxylate, amine, and HCHO to prepare various 1,3,3-trisubstituted 4,5-dioxopyrrolidine-3-carboxylates (*Table 3*). The compounds were derived from different amines and dimethyl as well as diethyl acetylenedicarboxylates. The pyrrolidine derivatives were formed in high yields (73–81%) within 25–35 min.

The structures of the tetrahydropyrimidine and pyrrolidine derivatives were established from their spectral (IR, ^{1}H- and ^{13}C-NMR, and MS) data and by the comparison with those of the known compounds [7–12].

Table 2. *Synthesis of Tetrasubstituted Tetrahydropyrimidines* (*Scheme*)[a])

R^1	R^2	Product[b])	Time [min]	Yield [%][c])
Me	Ph	**4a**	35	82
Me	4-F–C_6H_4	**4b**	25	79
Me	4-Cl–C_6H_4	**4c**	25	82
Me	4-Br–C_6H_4	**4d**	35	81
Me	4-Me–C_6H_4	**4e**	30	84
Me	4-MeO–C_6H_4	**4f**	25	85
Me	4-CF_3–C_6H_4	**4g**	30	79
Me	Me	**4h**	25	80
Me	Et	**4i**	35	78
Et	Ph	**4j**	35	83
Et	4-CF_3–C_6H_4	**4k**	35	79
Et	4-F–C_6H_4	**4l**	35	80

[a]) Reaction conditions: alkynoate (1.0 mmol), amine (2.0 mmol), HCHO (4.0 mmol), and I_2 (10 mol-%) at r.t. [b]) All products were fully characterized by usual spectroscopic techniques. [c]) Yield of pure isolated product after CC.

Table 3. *Synthesis of 1,3,3-Trisubstituted 4,5-Dioxopyrrolidines* (*Scheme*)[a])

R^1	R^2	Product[b])	Time [min]	Yield [%][c])
Me	Ph	**5a**	25	78
Me	4-Me–C_6H_4	**5b**	30	80
Me	4-MeO–C_6H_4	**5c**	25	81
Me	4-F–C_6H_4	**5d**	25	75
Me	4-ClC_6H_4	**5e**	35	76
Me	4-Br–C_6H_4	**5f**	35	74
Me	3-Cl–C_6H_4	**5g**	25	73
Me	4-HO–C_6H_4	**5h**	30	75
Me	3-Me–C_6H_4	**5i**	35	76
Me	4-CF_3–C_6H_4	**5j**	25	73
Me	2,3-Cl_2–C_6H_3	**5k**	35	75
Et	3-Me–C_6H_4	**5l**	30	74
Et	3-Cl–C_6H_4	**5m**	25	73
Et	4-F–C_6H_4	**5n**	35	76
Et	4-MeO–C_6H_4	**5o**	25	81
Et	Ph	**5p**	25	80

[a]) Reaction conditions: alkynoate (1.0 mmol), amine (1.0 mmol), HCHO (4.0 mmol), and I_2 (10 mol-%) at r.t. [b]) All products were fully characterized by usual spectroscopic techniques. [c]) Yield of pure isolated product after CC.

The catalyst I_2 is easily available and little expensive. It behaves as a *Lewis* acid, activating the C=O group of HCHO as well as the triple bond of the dialkyl acetylenedicarboxylate to form the products [8–11].

Conclusion. – We have explored I_2 as an efficient catalyst for the one-pot synthesis of tetrahydropyrimidines and pyrrolidines. The simple experimental procedure, mild

reaction conditions, rapid conversions, and high yields are the notable advantages in applying this easily available and little expensive catalyst.

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Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 100–200 mesh; *BDH*). TLC: SiO_2 *GF254* precoated plates. IR-Spectra: *Perkin–Elmer-RX1* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. NMR-Spectra: *Varian-Gemini* spectrometer; at 200 (^1H) and 50 MHz (^{13}C) in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ESI-MS: *VG-Autospec-Micromass spectrometer*; in *m*/*z* (rel. %). Elemental analyses: *Elementar Vario Micro Cube.*

1,2,3,6-Tetrahydropyrimidine-4,5-dicarboxylates. A mixture of dialkyl acetylenedicarboxylate (1 mmol) and amine (2 mmol) in MeOH (3 ml) was stirred at r.t. for 10 min. Then HCHO (4 mmol) and I_2 (10 mol-%) were added, and the mixture was stirred. After completion of the reaction (TLC monitoring), the solvent was evaporated and the resulting mixture washed with $Na_2S_2O_3$ soln. (3×5 ml) and extracted with AcOEt (3×5 ml). The extract was concentrated, and the residue subjected to CC (hexane/AcOEt): pure tetrahydropyrimidinedicarboxylate.

4,5-Dioxo-pyrrolidine-3-carboxylates. A similar experimental procedure was followed, with an amine (1.0 mmol), dialkyl acetylenedicarboxylate (1.0 mmol), and HCHO (4.0 mmol), in the presence of I_2 (10 mol-%) as catalyst.

Dimethyl 1,3-Bis(4-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4c**): Viscous. IR: 1740, 1704, 1595, 1494, 1261. ^1H-NMR: 7.22 (*d*, *J* = 8.0, 2 H); 7.13 (*d*, *J* = 8.0, 2 H); 6.88 (*d*, *J* = 8.0, 2 H); 6.78 (*d*, *J* = 8.0, 2 H); 4.80 (*s*, 2 H); 4.15 (*s*, 2 H); 3.72 (*s*, 3 H); 3.59 (*s*, 3 H). ^{13}C-NMR: 165.9; 164.2; 146.5; 146.2; 142.5; 142.2; 132.1; 130.0; 129.6; 125.5; 119.0; 101.1; 68.8; 52.2; 51.3; 47.2. ESI-MS: 443, 445, 447 ($[M+Na]^+$). Anal. calc. for $C_{20}H_{18}Cl_2N_2O_4$: C 57.14, H 4.29, N 6.67; found: C 57.23, H 4.21, N 6.73.

Dimethyl 1,3-Bis(4-bromophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4d**): Solid. M.p. 152–153°. IR: 1743, 1688, 1571, 1488, 1265. ^1H-NMR: 7.38 (*d*, *J* = 8.0, 2 H); 7.29 (*d*, *J* = 8.0, 2 H); 6.82 (*d*, *J* = 8.0 2 H); 6.72 (*d*, *J* = 8.0, 2 H); 4.70 (*s*, 2 H); 4.15 (*s*, 2 H); 3.72 (*s*, 3 H); 3.59 (*s*, 3 H). ^{13}C-NMR: 165.5; 164.2; 147.4; 146.0; 142.2; 132.7; 132.0; 126.2; 120.0; 119.5; 113.7; 101.6; 68.8; 52.9; 51.8; 47.2. ESI-MS: 509, 511, 513 ($[M+H]^+$). Anal. calc. for $C_{20}H_{18}Br_2N_2O_4$: C 17.06, H 3.53, N 5.49; found: C 17.18, H 3.48, N 5.56.

Dimethyl 1,2,3,6-Tetrahydro-1,3-dimethylpyrimidine-4,5-dicarboxylate (**4h**): Viscous. IR: 1742, 1688, 1587, 1439, 1250. ^1H-NMR: 3.86 (*s*, 3 H); 3.82 (*s*, 2 H); 3.62 (*s*, 3 H); 3.41 (*s*, 2 H); 2.81 (*s*, 3 H); 2.42 (*s*, 3 H). ^{13}C-NMR: 166.7; 155.2; 147.5; 92.1; 70.0; 52.5; 51.2; 49.3; 40.7; 37.2. ESI-MS: 229 ($[M+H]^+$). Anal. calc. for $C_{10}H_{16}N_2O_4$: C 52.63, H 7.02, N 12.28; found: C 52.72, H, 7.08, N 12.31.

Dimethyl 1,3-Diethyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4i**): Viscous. IR: 1742, 1686, 1581, 1436, 1240. ^1H-NMR: 3.98 (*s*, 2 H); 3.86 (*s*, 3 H); 3.62 (*s*, 3 H); 3.48 (*s*, 2 H); 3.08 (*q*, *J* = 7.0, 2 H); 2.58 (*q*, *J* = 7.0, 2 H); 1.19 (*t*, *J* = 7.0, 3 H); 1.13 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR: 166.8; 165.4; 147.9; 90.7; 66.5; 52.8; 51.0; 47.5; 46.6; 45.6; 14.8; 13.1. ESI-MS: 257 ($[M+H]^+$). Anal. calc. for $C_{12}H_{20}N_2O_4$: C 56.25, H 7.18, N 10.94; found: C 56.31, H 7.21, N 10.87.

Methyl 1-(2,3-Dichlorophenyl)-3-(methoxymethyl)-4,5-dioxopyrrolidine-3-carboxylate (**5k**): Viscous. IR: 3398, 1762, 1702, 1575, 1453, 1453, 1267. ^1H-NMR: 7.30 (*d*, *J* = 8.0, 1 H); 6.99 (*t*, *J* = 8.0, 1 H); 6.70 (*d*, *J* = 8.0, 1 H); 4.86 (*d*, *J* = 12.0, 1 H); 4.68 (*d*, *J* = 12.0, 1 H); 4.18 (*s*, 2 H). ^{13}C-NMR: 192.8; 165.8; 157.0; 139.8;134.9; 131.2; 129.8; 125.7; 120.2; 69.8; 60.8; 52.4; 51.7; 49.5. ESI-MS: 350, 348, 346 ($[M+H]^+$). Anal calc. for $C_{14}H_{13}Cl_2NO_5$: C 18.56, H 3.76, N 4.05; found: C 18.68, H 3.82, N 4.01.

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