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Regioselective synthesis of 5-alkylidene and 5-(iodoalkylidene)-pyrrol-2(5*H*)-ones by halolactamisation of (2*Z*,4*E*)-dienamides and (*Z*)-alk-2-en-4-ynamides

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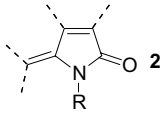
Abstract—Stereo- and regioselective synthesis of 5-alkylidene (arylidene) and 5-(iodoalkylidene)-pyrrol-2(5*H*)-ones was achieved from (2*Z*,4*E*)-dienamides and (*Z*)-alk-2-en-4-ynamides by halocyclisation reaction. Selectivity was found to be highly dependent on the nature of the substituents and on the temperature.



5-Ylidene pyrrol-2(5*H*)-one structural unit **2** is found in a range of biologically important natural products including holomycin,[1] pukeleimide,[2] isoampullicin[3] and the bile pigment bilirubin.[4] Although extensive methodology has been developed for the construction of 5-ylidene furan-2(5*H*)-ones and 4-ylidene tetronic acids,[5] only a few examples are reported for the preparation of 5-ylidene pyrrol-2(5*H*)-ones **2**.[6] Nevertheless, although *Z*-selectivity of the exocyclic double bond is relatively easy to control, clean access to the (*E*)-stereoisomer still remains a challenge for organic chemists. We recently reported the regioselective synthesis of α-pyrones and α-pyridones under palladium complex catalysis by coupling tributylstannylallenes with (*Z*)-iodovinylic acids or (*Z*)-iodovinylic amides.[7,8] We have also previously described the synthesis of dienoic acids and enynoic acids from β-iodovinylic acids and vinyltins and alkynylzinc reagents, respectively.[9] This methodology was then applied to the synthesis of 5-alkylidene (arylidene)-furan-2(5*H*)-ones.[10]

In connection with our studies on the synthesis of oxygen- and nitrogen-containing heterocycles, we wish to report the electrophilic cyclisation of dienamides and enynamides with ICl as regioselective method for synthesising 5-alkylidene and 5-(iodoalkylidene)-pyrrol-2(5*H*)-ones, respectively. We first examined the reaction of our (2*Z*,4*E*)-dienamides **1** using several electrophilic halogen sources (ICl, I_2, I_2/KI, NBS, ...). The dienamides **1** were obtained in excellent yields by treatment of the corresponding (2*Z*,4*E*)-dienoic acids[9d] with oxalyl chloride followed by addition of primary amine.[11] ICl was found to be the best reagent to obtain fair to good yields of 5-alkylidene pyrrol-2(5*H*)-ones **2**. The use of other sources of halogen (NIS, NBS, I_2/KI, ...) led to lower yields. A number of solvents were examined including ether, THF, acetonitrile, toluene and dichloromethane. The latter gave the best results, which we think may be due to a greater ability to solubilise ICl. Interestingly, the cyclisation is followed by in-situ dehydrohalogenation leading to 5-alkylidene pyrrol-2(5*H*)-ones **2a**–**g**. This takes place without any addition of base (Scheme 1 and Table 1), as opposed to what was observed previously when we prepared γ-alkylidene butenolides by halolactonisation of dienoic acids, where

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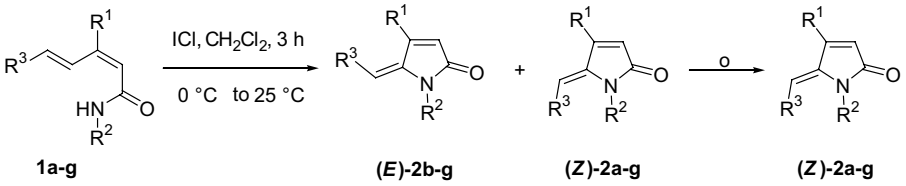


Scheme 1.

Table 1. Synthesis of 5-alkylidene (arylidene)-pyrrol-2(5*H*)-ones **2a**–**g**

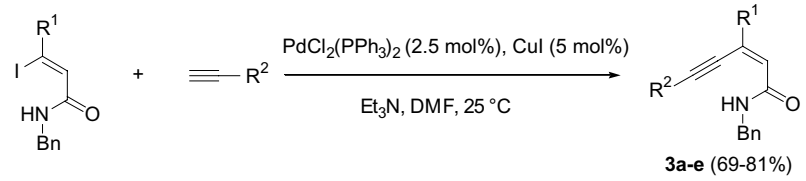
Entry	R^1	R^2	R^3	Pyrrol-2(5*H*)-one	Yield (%)	*Z*/*E*[a]	*Z*/*E*[b]
1	Ph	Bn	Ph	**2a**	55	100/0	100/0
2	Ph	Bn	Me_3Si	**2b**	80	10/90	100/0
3	Ph	$(CH_3)_2CH–\overset{*}{C}H–CH_3$	Me_3Si	**2c**	77	5/95	100/0[c]
4	H	$PhCH(CH_3)$	Me_3Si	**2d**	58	6/94	78/22
5	CH_3	Bn	Me_3Si	**2e**	78	3/97	100/0
6	CH_3	*m*-$CH_3O–C_6H_4$	Me_3Si	**2f**	50	5/95	100/0
7	CH_3OCH_2	*m*-$CH_3O–C_6H_4$	Me_3Si	**2g**	51	7/93	100/0

[a] Before isomerisation reaction.
[b] After a spontaneous isomerisation.
[c] $[\alpha]_D^{25} + 29^\circ$ ($c = 2\%$, CH_2Cl_2).

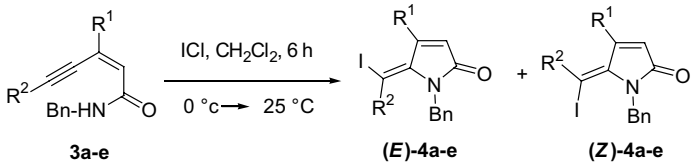
it was necessary to use a base such as the DBU to form the exocyclic double bond.[10] The results are summarised in Table 1.

As expected, the selectivity observed was largely in favour of the (*E*)-stereochemistry of the exocyclic double bond. Nevertheless, selectivity was highly dependent on temperature and the nature of the substituent. For the first time, γ-silylmethylidene pyrrol-2(5*H*)-ones **2b**–**g** were obtained with mainly *E* stereochemistry for the exocyclic double bond, which was confirmed by NOESY experiments. It should be noted that at room temperature **2b**–**g** isomerised quickly (after few hours) largely in favour of *Z* stereochemistry. In the case of the formation of **2a**, the desired benzylidene pyrrol-2(5*H*)-one was obtained only with a complete (*Z*)-configuration of the exocyclic double bond. This can be explained by the greater thermodynamic stability of the (*Z*)-isomer of **2a** compared to (*E*)-**2a** where the extensive interaction of the ortho hydrogens of the phenyl group and the phenyl substituent prevents conjugation. As shown in Table 1, we obtained optically pure γ-silylmethylidene pyrrol-2(5*H*)-ones **2c** from the available optically active amide **1c** (entry 3), and in all cases the γ-alkylidene pyrrol-2(5*H*)-ones **2** were obtained without any trace of 2-pyridone. It should be noted that the alkylidene pyrrol-2(5*H*)-ones were not stable and gradually decomposed upon heating or exposure to air. It was also necessary to neutralise silica during chromatography using a base such as triethylamine to avoid their decomposition.

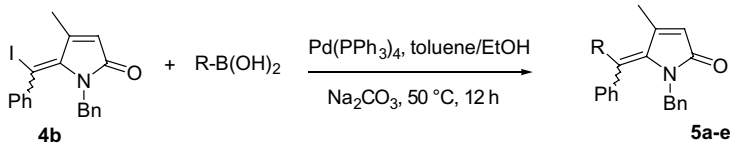
We next chose to extend our method by investigating similar cyclisation of (*Z*)-alk-2-en-4-ynamides **3a**–**e**. Alk-2-en-4-ynamides **3a**–**e** were prepared via the Sonogashira cross-coupling reaction[12] of terminal alkynes with (*Z*)-3-iodoalk-2-enamides (Scheme 2). The mild



Scheme 2.



Scheme 3.



5a: R = *p*.CH_3-C_6H_4, *E*/*Z* = 90/10(71%); **5b**: R = 3-thienyl,*E*/*Z* = 75/25(65%); **5c**: R = tert.butylvinyl, *5E*/*5Z* = 10/90(62%); **5d**: R = *p*.Br-C_6H_4, *E*/*Z* = 88/12 (67%); **5e**:R = *m*.Cl-C_6H_4, *E*/*Z* = 85/15(60%).

Scheme 4.

Table 2. Synthesis of (iodoalkylidene)-pyrrol-2(5*H*)-ones **4a**–**e**

Entry	R^1	R^2	Product	*E*/*Z*	Yield (%)
1	H	Ph	**4a**	90/10	65
2	CH_3	Ph	**4b**	65/35	79
3	Ph	Ph	**4c**	55/45	80
4	CH_3	Me_3Si	**4d**	85/15	75
5	CH_3	$HOC(CH_3)_2$	**4e**	90/10	70

experimental conditions of the reaction resulted in excellent yields of (*Z*)-enynamides and no polymerisation products were detected.

Indeed, treatment of (*Z*)-alk-2-en-4-ynamides **3a**–**e** by ICl in CH_2Cl_2 gave good yields of regioselective 5-(iodoalkylidene or arylidene)-pyrrol-2(5*H*)-ones **4a**–**e** (Scheme 3 and Table 2).[13] In our case, this iodocyclisation reaction proceeded via the 5-*exo* process, and the corresponding six-membered ring lactams were not observed in either case. The exocyclic double bond formed had mainly the *E* configuration except in the case of **4b** and **4c** (Table 2, entries 2 and 3), where a significant amount of *Z*-isomer were observed.

Finally, Suzuki cross-coupling[14] of **4b** with vinyl or aryl boronic acids using toluene as solvent, ethanol as co-solvent and 3 mol% of tetrakis(triphenylphosphine)palladium(0) as catalyst allowed the stereoselective synthesis of desired products **5a**–**e** (Scheme 4).[15] The use of (*E*)-tertiobutyl vinyl boronic acid reagent permitted the transfer of a vinyl group with retention of the configuration of the double bond, and no polymerisation products were observed.

In conclusion, we describe here efficient and general syntheses of 5-alkylidene (or arylidene) and 5-(iodoalkylidene or arylidene)-pyrrol-2(5*H*)-ones by halolactamisation of unsaturated amides. Further studies are currently in progress aimed at broadening the application of iodoalkylidene lactams to the synthesis of natural alkylidene pyrrolones.

Acknowledgements

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13. Typical procedure: Preparation of **2a**–**g** or **4a**–**e**. Iodine monochloride (1.7 g, 10.5 mmol) in dry dichloromethane (10 mL) was added dropwise at 0 °C to dieneamide **1** (or enynamide **3**) (10 mmol). Stirring was then maintained for 3 h at room temperature in darkness, the mixture was hydrolysed by dropwise addition of a 5% solution of sodium thiosulfate until the solution became clear. The solution was then extracted with CH_2Cl_2 (3×15 mL) and dried with $MgSO_4$. After evaporation of the solvent, the products were obtained after purification by flash column chromatography on silica (petroleum ether/diethyl ether/triethylamine; 80/19/1) or by crystallisation in diethyl ether to yield alkylidene pyrrol-2(5*H*)-one **2** or iodoalkylidene pyrrol-2(5*H*)-one **4**. For example: Compound (***Z***)-**2e**: IR (neat): 2954, 1672, 1611; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 0.21 (s, 9H), 1.98 (s, 3H), 4.64 (s, 2H), 4.85 (s, 1H), 6.18 (s, 1H), 7.19–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): −0.04 (3C), 12.3, 52.2, 103.5, 122.3, 127.2, 128.4 (2C), 128.9 (2C), 139.8, 147.5, 161.6, 164.3; MS (70 eV, EI) *m*/*z*: 271 (M, 4), 243 (22), 91 (100), 73 (16), 65 (20). (***E***)-**4b**: IR (neat): 3065, 2964, 1677, 1603; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.55 (s, 3H), 4.46 (s, 2H), 6.47 (s, 1H), 7.22–7.56 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 19.0, 52.5, 74.3, 127.1, 127.2, 128.3 (2C), 128.5 (2C), 128.8 (2C), 129.8, 130.3 (2C), 140.5, 141.6, 147.2, 152.3, 157.7; MS (70 eV, EI) *m*/*z* (%): 401 (M, 0.4), 127 (6), 91 (100), 65 (18), 64 (17), 48 (11). (***Z***)-**4b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.61 (s, 3H), 4.51 (s, 2H), 6.34 (s, 1H), 7.22–7.56 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 19.5, 54.6, 74.2, 126.9, 127.2, 128.0 (2C), 128.6 (2C), 128.8 (2C), 129.3, 130.5 (2C), 140.4, 141.1, 146.1, 151.9, 157.6.
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15. Typical procedure: Preparation of **5a**–**e**. An oven-dried Schlenk flask was evacuated and back-filled with argon and charged with ethanol (8 mL), toluene (10 mL), pyrrolone **4b** (5 mmol), and aryl boronic acid (6 mmol). The flask was evacuated and back-filled with argon and then 0.6 mL of 1 M solution of Na_2CO_3 and $Pd(PPh_3)_4$ (173 mg, 0.15 mmol, 3 mol%), were added. The reaction mixture was stirred at 50 °C for 12 h, the solution was filtered through a Celite pad and the solvents were evaporated. The residue was extracted with diethylether, and dried over anhydrous $MgSO_4$. Products **5a**–**e** were obtained after purification by flash column chromatography on silica (petroleum ether/diethyl ether/triethylamine; 80/19/1). For example: (*E*)-1-benzyl-4-methyl-5(phenyl-*p*-tolylmethylene)-pyrrol-2(5*H*)-one **5a**. (***E***)-**5a**: IR (neat): 3028, 2964, 1673, 1604; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.53 (d, $J = 1.4$ Hz, 3H), 2.45 (s, 3H), 4.74 (s, 2H), 6.29 (q, $J = 1.4$ Hz, 1H), 7.23–7.46 (m, 14H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 15.8, 21.8, 52.5, 115.8, 124.4, 127.1, 127.9, 128.3 (2C), 128.4 (2C), 128.8 (2C), 129.5 (2C), 130.6 (2C), 131.6 (2C), 135.3, 138.5, 139.3, 141.0, 148.0, 150.5, 160.1; MS (70 eV, EI) *m*/*z* (%): 365 (M, 35), 275 (21), 274 (100), 165 (17), 105 (22), 65 (24), 39 (13). (***Z***)-**5a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.55 (s, 3H), 2.44 (s, 3H), 4.73 (s, 2H), 6.34 (br s, 1H), 7.20–7.49 (m, 14H).