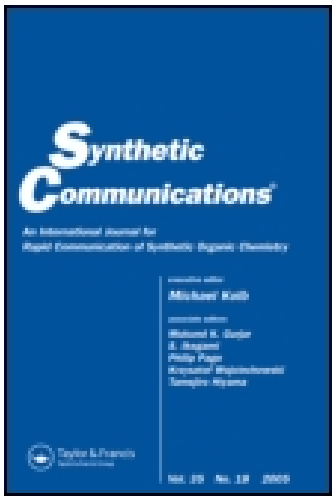

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AN EFFICIENT SYNTHESIS OF 1,4-OXAZEPINES FROM β-FORMYL ENAMIDE USING I_2-$NaHCO_3$ SYSTEM

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AN EFFICIENT SYNTHESIS OF 1,4-OXAZEPINES FROM β-FORMYL ENAMIDE USING I_2-$NaHCO_3$ SYSTEM

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ABSTRACT

A new and efficient method for synthesis of 1,4-oxazepine has been developed utilizing I_2-$NaHCO_3$ promoted intramolecular cyclisation of *N*-progargyl-β-hydroxylmethyl enamide. The method is mild and simple.

The 1,4-oxazepines constitute the parent core of many pharmaceutical compounds such as loxapine, nitroxapine hydrochloride, linadryl-H and related products.[1] They find wide application in the asymmetric synthesis of monoterpenoid alkaloids and secoiridoids.[2] The construction of this structural unit would be useful and indeed, several approaches have been reported.[3] However, these methods comprise certain disadvantages which include harsh reaction conditions[4] or use of highly reactive reagents[5] and therefore development of protocol using mild and readily available reagents

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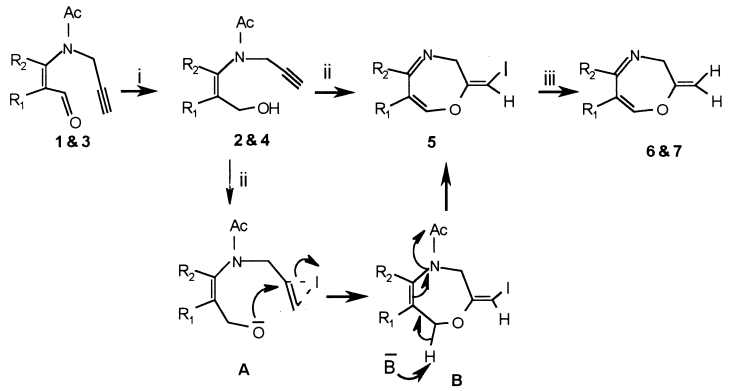
is needed. The reagent system I_2-$NaHCO_3$ has been considered as a mild albeit powerful tool[6] for iodolactonization of γ-unsaturated acids,[7] iodoetherification of γ-unsaturated alcohol[8] and iodolactamization of *N*-substituted carbamates.[9] This strategy has played a key role in the synthesis of natural products including estrone-taloromycin[10] and fungal metabolites.[11] However, the literature reports limit the applications of I_2-$NaHCO_3$ system within 1,5- or 1,6-cyclisations utilizing olefinic double bonds.[6–10]

Recently, we have documented the development of β-formyl enamide as an organic synthon in Diels–Alder reaction[12] and diyne formation.[13] In particular, β-formyl enamide has emerged as a valuable precursor for a number of functionalised pyridines.[14] The encouraging results prompted us to explore its synthetic utility for other biologically potential heterocycles. In continuation of our interests,[15] we present here a mild and facile approach for preparation of 1,4-oxazepines from *N*-propargyl-β-hydroxymethyl enamides using I_2-$NaHCO_3$ system.

In a representative experiment, to a solution of 3β-acetoxy-17-(*N*,*N*-propargylacetamido)-16-formyl-androst-5,16-diene (**1a**, 10 mmol)[13] in methanol (20 ml) was added $NaBH_4$ (10 mmol) at room temperature under nitrogen for 1 h. On completion of reaction, it was concentrated under reduced pressure and purified by silica-gel column chromatography to afford 3β-acetoxy-17-(*N*,*N*-propargylacetamido)-16-hydroxymethyl-androst-5,16-diene (**2a**) in 90% yield. Stirring of **2a** (1 mmole) with iodine (5 mmole) and $NaHCO_3$ (10 mmole) in a mixture of diethyl-ether (40 ml) and water (10 ml) for 8 h at room temperature followed by treatment[16] with aqueous Na_2SO_3 afforded **6a** in 88% yield (Scheme 1). The ^{1}H NMR



Scheme 1. Reagents i) $NaBH_4$/MeOH/0–10°C; ii) I_2-$NaHCO_3$/Et_2O-H_2O/r.t.; iii) Na_2SO_3-H_2O.

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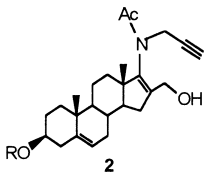
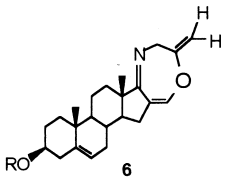
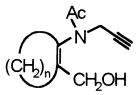
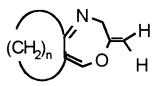
Table. I_2-$NaHCO_3$ Mediated Cyclisation of *N*-Propargyl-β-hydroxymethylenamide

Entry	Substrate[a]	Time/h	Product[b]	Yield[c] (%)
1	 **2a**, R = Ac	3	 **6a**, R = Ac	88
2	**2b**, R = Bz	3.5	**6b**, R = Bz	85
3	**2** **2c**, R= Me	3	**6** **6c**, R= Me	82
4	 **4a**, n= 4	3.5	 **7a**, n= 4	79
5	**4** **4b**, n= 5	4	**7** **7b**, n= 5	68

[a]Obtained by $NaBH_4$ reduction of corresponding aldehydes. [b]All products spectra consistent with the assigned structure.
[c]Isolated yields.

of **6a** showed loss of *N*-acetyl group and appearance of two triplet signals at δ 5.20 and 4.94 for geminal olefinic protons (J = 1.4 Hz) and a singlet signal at 7.42 for conjugated imine proton of 1,4-oxazepine ring. Similarly steroidal *N*-propargyl-β-hydroxymethylenamide (**2b–c**) afforded products **6b–c** in excellent yields.

In an effort to generalize the cyclisation reaction, the β-hydroxymethylenamides of cycloalkanes (**4a–b**) were prepared from corresponding β-formyl enamides by reduction with $NaBH_4$ in excellent yields (92–94%). Similarly, cyclisation reactions of **4a–b** promoted by I_2-$NaHCO_3$ afforded 1,4-oxazepines (**7a–b**) in 68–79% yields.

The product obtained indicated a mechanism of sequential process involving 1,7-cyclisation, deacetylation and reductive dehalogenation reactions. As a first step, the propargyl group undergoes an electrophilic attack by iodine[7] to the intermediate iodonium ion (**A**) which would undergo a nucleophilic attack of an alkoxide anion,[10] generated *in situ*, to afford iodomethylene-1,4-oxazepine intermediate (**B**). Subsequent attack of base HCO_3^- on methylene proton linked to oxygen atom led to loss of acetaldehyde to form iodoalkene **5** followed by dehalogenation with sodium sulfite to afford 1,4-benzoxazepine **6**. The isolation of acetaldehyde render further support to our proposed mechanistic pathway.

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In conclusion, an efficient application of β-formyl enamide is described for convenient preparation of 1,4-oxazepines involving a 1,7-cyclisation reaction. The use of I_2-$NaHCO_3$ provides a mild and simple strategy for high yield preparation of 1,4-oxazepines.

EXPERIMENTAL

Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra were recorded by using a Perkin Elmer 237 and 580B spectrometers in KBr discs. ^{1}H NMR spectra were recorded in Varian T-60 and Bruker 300 MHz spectrometer. Mass spectra were recorded on a Incos 50 mass spectra machine. Elemental analysis were obtained from a Perkin Elmer Series II 2400 machine. *N*-Propargyl-β-formyl enamides were prepared according to a reported procedure.[15a]

General Procedure for Reduction of 3β-Acetoxy-16-formyl-17-(*N*,*N*-propargylacetamido)-androst-5,16-diene (1a)

To a solution of *N*-propargyl-β-formyl enamide (**1a**, 438 mg, 1 mmol) in methanol (20 ml) was added $NaBH_4$ (380 mg, 10 mmol) in small portions at 0°C and the reaction mixture was stirred at same temperature for 1 h. On completion of reaction it was poured into ice–cold water (200 ml) and extracted with CH_2Cl_2 (3×25 ml). The organic portion was separated, washed with water and dried over Na_2SO_4. Removal of solvent gave a white solid which was purified by column chromatography using $CHCl_3$/MeOH: 95/5 as eluant to afford 3β-acetoxy-16-(hydroxymethyl)-17-(*N*-propargylacetamido)-androst-5,16-diene (**2a**) as white crystals ($CHCl_3$), yield 418 mg (95%), mp 198–199°C, Rf = 0.15 in $CHCl_3$. IR (KBr) ν 3410, 3235, 2915, 2150, 1725, 1630, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.48 (1H, bs), 4.50 (1H, bs), 4.20 (2H, t), 4.0 (1H, m), 3.80 (1H, m), 1.89 (3H, s), 1.58 (3H, s), 1.02 (3H, s), 0.88 (3H, s), 2.20–1.30 (22H, m); MS: *m*/*z* 439 ($M^+ + H$), 438 (M^+), 408, 366. Anal. Calcd. for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48; N, 3.19. Found: C, 73.89; H, 8.69; N, 3.70.

Cyclisation of 3β-Acetoxy-16-(hydroxymethyl)-17-(*N*,*N*-propargylacetamido)-androst-5,16-diene (2a)

A mixture of **2a** (440 mg, 1 mmol), $NaHCO_3$ (840 mg, 10 mmol) and iodine (1.27 g, 5 mmol) were taken in ether (40 ml) and water (10 ml) and

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stirred under N_2 atmosphere at room temperature for 8 h. The reaction was monitored vide silica gel TLC. On completion of reaction, it was extracted with CH_2Cl_2 (3×50 ml) and the combined organic portion was washed with a saturated solution of Na_2SO_3. Removal of the solvent gave a brownish product which was purified by column chromatography over neutral alumina eluting with hexane/EtOAC: 95/5 system to afford 1,4-oxazepine (**6a**) as white crystals, yield 348 mg (88%), Rf = 0.6 (10% EtOAC/hexane): mp 162–163°C; IR (KBr) ν 2990, 1735, 1645, 1375, 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.68 (1H, s), 5.40 (1H, bs), 5.20 (1H, t, J = 1.4 Hz), 4.94 (1H, t, J = 1.4 Hz), 4.62 (1H, m), 2.60–1.09 (19H, m), 2.03 (3H, s), 1.06 (3H, s), 0.92 (3H, s); MS: *m/z* 395 (M^+), 335 (M^+-CH_3COOH). Anal. Calcd. for $C_{25}H_{33}NO_3$: C, 74.91; H, 8.40; N, 3.54. Found: C, 74.42; H, 8.70; N, 3.94.

6b, yield 388 mg (85%), Rf = 0.6 (10% EtOAC/hexane): mp 170–172°C; IR (KBr) ν 2990, 1720, 1640, 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.90–7.10 (6H, m), 5.60 (1H, t, 1.50 Hz), 5.40 (1H, bs), 5.10 (1H, t, J = 1.5 Hz), 4.50 (1H, m), 2.20–0.90 (19H, m), 1.00 (3H, s), 0.80 (3H, s); MS: *m/z* 457 (M^+), 335 (M^+-PhCOOH). Anal. Calcd. For $C_{30}H_{35}NO_3$: C, 78.74; H, 7.71; N, 3.06. Found: C, 78.54; H, 7.58; N, 3.24.

6c, yield 301 mg (82%), Rf = 0.55 (10% EtOAC/hexane): mp 165–167°C; IR (KBr) ν 2980, 1725, 1635, 1280 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40 (1H, m), 5.50 (1H, t, 1.50 Hz), 5.30 (1H, bs), 5.10 (1H, t, J = 1.5 Hz), 4.55 (1H, m), 3.20 (3H, s), 2.20–0.95 (19H, m), 1.00 (3H, s), 0.80 (3H, s); MS: *m/z* 367 (M^+). Anal. Calcd. For $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.64; H, 8.88; N, 3.98.

7a, 129 mg (79%), Rf = 0.5 (10% EtOAC/hexane): mp 102–103°C; IR (KBr) ν 2980, 1640, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (1H, t, J = 1.4 Hz), 5.22 (1H, t, J = 1.4 Hz), 4.92 (1H, t, J = 1.4 Hz), 2.54–0.85 (10H, m); MS: *m/z* 163 (M^+), 162. Anal. Calcd. For $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.42; H, 7.80; N, 8.44.

7b, 120 mg (68%), Rf = 0.5 (10% EtOAC/hexane) mp 100–101°C; IR (KBr) ν 2980, 1640, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (1H, t, J = 1.4 Hz), 5.35 (1H, t, J = 1.4 Hz), 4.85 (1H, t, J = 1.4 Hz), 2.64–0.75 (12H, m); MS *m/z* 177 (M^+), 176. Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.61; H, 8.37; N, 8.02.

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16. Compound **5** was found to be an unstable product, which decomposes under aerobic condition. Reduction with Na_2SO_3 provided a comparatively stable product **6**.

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