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Tetrahedron Letters 48 (2007) 6674–6676
Tetrahedron Letters

Selective amidoalkylation of cyclic enamino ketones with *N*-acyliminium salts of 3,4-dihydroisoquinolines

Stela Statkova-Abeghe,* Plamen A. Angelov, Iliyan Ivanov, Stoyanka Nikolova and Ekaterina Kochovska

Department of Organic Chemistry, University of Plovdiv, 24 'Tsar Assen' str., 4000 Plovdiv, Bulgaria

Received 8 June 2007; revised 10 July 2007; accepted 19 July 2007
Available online 27 July 2007

Abstract—A series of cyclic enaminoketones were selectively amidoalkylated at the α-carbon in reactions with acyliminium reagents derived from 3,4-dihydroisoquinolines.

The α-amidoalkylation of carbon nucleophiles with *N*-acyliminium compounds is a long-established method for C–C bond formation.[1] *N*-Acyliminium salts of isoquinoline and 3,4-dihydroisoquinoline, in particular, have been successfully used in reactions with heteroaromatic[2] and active methylene nucleophiles.[3] As a part of a project aimed at the synthesis of diverse pyrimido[6,1-*a*]isoquinolines,[4] which are interesting for their biological activity,[5] we had reasons to investigate the reactivity of *N*-acyliminium compounds **2** derived from 3,4-dihydroisoquinolines **1** towards enaminones **3**. Enaminones, as defined by Greenhill, are monoenamines of 1,3-dicarbonyl compounds[6] and they combine the ambident electrophilicity of enones with the ambident nucleophilicity of enamines. With three sites susceptible to electrophilic attack, it is difficult to predict the outcome of such a reaction in terms of regioselectivity. Despite numerous studies on the chemistry of enaminones[6,7] and their wide application in the synthesis of heterocycles,[7a,c] to the best of our knowledge, no information is available for reactions of enaminones with *N*-acyliminium compounds. In this Letter, we describe the first examples of this type of reaction.

To determine the influence of the acyl component, we initially studied the reactions of three different *N*-acyliminium compounds (**2a**–**c**) with enaminone **3**, ($R^3 = CH_2C_6H_5$, $R^2 = CH_3$). The reactions were carried out for 1 h at reflux in 1,2-dichloroethane. As indicated in Table 1, the best yields were obtained when $R^1 = OEt$. These results are in good agreement with what is known from previous studies on other carbon nucleophiles.[1] Accordingly, we proceeded with EtO-COCl as the acyl component while varying the substituents R^3 and R^2 in a series of enaminones (**3d**–**l**).[8] The yields varied from moderate to good (Table 1) and all of the examples studied proceeded regioselectively at the α-carbon of the enaminone as indicated by the disappearance of the characteristic vinyl signal in the ^1H NMR spectra. No reaction at *N* or *O* was detected. The main problem leading to incomplete conversion of the starting materials was the formation of HCl salts of the enaminones, which prevented further reaction. Attempts to use Et_3N as a HCl scavenger, however, improved the yields only when the substituent R in the acyliminium reagent was CH_3O. This reagent system showed much higher reactivity, which allowed the reactions to be carried out at rt.

Attempts to apply the above conditions to a series of acyclic enaminones obtained from acetylacetone and amines (R^3NH_2) were not successful as the selectivity was rather poor and complex mixtures of products were formed.

Once the C–C bond between the isoquinoline and the enaminone moieties had been formed, cyclization to pyrimidoisoquinoline type structures could easily be achieved with the aid of a strong base when R^1 in **4** was an OEt group[9] (Scheme 2, Table 2).

* Corresponding author. Tel.: +359 32 261349; e-mail: stab@argon.acad.bg

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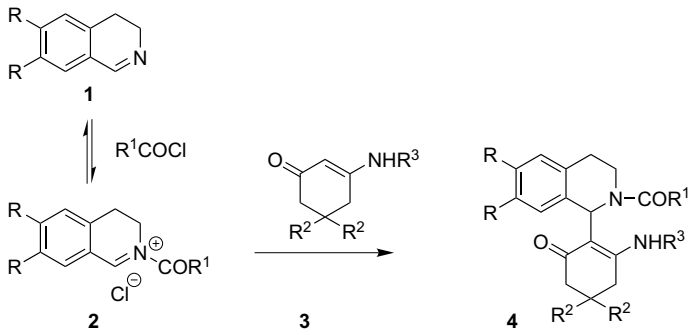
doi:10.1016/j.tetlet.2007.07.116

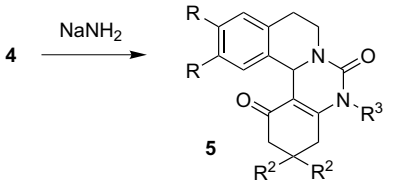


Scheme 1.

Table 1. Yields of compounds **4** obtained according to Scheme 1

4	R	R^1	R^2	R^3	Time (h)	Yield (%)
a	H	OC_2H_5	CH_3	$C_6H_5CH_2$	1	64
b	H	CH_3	CH_3	$C_6H_5CH_2$	1	50
c	H	C_6H_5	CH_3	$C_6H_5CH_2$	1	35
d	H	OC_2H_5	CH_3	$C_6H_5CH_2CH_2$	1	78
e	H	OC_2H_5	CH_3	3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	1	50
f	H	OC_2H_5	H	3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	1	40
g	H	OC_2H_5	CH_3	C_6H_5	0.5	45
h	H	OC_2H_5	CH_3	CH_3	2	36
i	H	OC_2H_5	CH_3	C_2H_5	2	31
j	CH_3O	OC_2H_5	CH_3	C_6H_5	0.5	61
k	CH_3O	OC_2H_5	CH_3	$C_6H_5CH_2$	0.5	66
l	CH_3O	OC_2H_5	CH_3	$C_6H_5CH_2CH_2$	0.5	70

For reaction conditions see Ref. 8.



Scheme 2.

Table 2.

5	R	R^2	R^3	Yield (%)
d	H	CH_3	$C_6H_5CH_2CH_2$	85
k	CH_3O	CH_3	$C_6H_5CH_2$	70

In conclusion, we have described the first regioselective amidoalkylation of enaminones with *N*-acyliminium reagents. The compounds obtained in this way are susceptible to further modifications, providing an entry towards structures with potential biological activity. Studies with different acyliminium reagents and enaminones are underway and the results will be reported in due course.

Acknowledgement

We acknowledge financial support from the fund for scientific research of Plovdiv University.

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8. *Synthesis of compounds* **4**, *general procedure*: Acid chloride (2 mmol) was added to a solution of the 3,4-dihydroisoquinoline (2 mmol) in 1,2-dichloroethane (5 mL) and the mixture was stirred for 30 min at rt The corresponding enaminone **3** (2 mmol) was then added and the reaction mixture was either heated at reflux for 1 h (when R = H) or kept at rt and Et_3N (2 mmol) dissolved in 1,2-dichloroethane

(3 mL) was slowly added over the course of 30 min (when R = OMe). The reaction mixture was quenched with 3% aq. HCl (60 mL) and extracted with dichloromethane (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed by distillation. Chromatographic purification was performed using neutral Al_2O_3 and diethyl ether or diethyl ether–petroleum as eluents. *Representative NMR data*: **4d**: ^{1}H NMR($CDCl_3$, 250 MHz, δ (ppm), J (Hz)): 1.01 (s, 3H), 1.02 (s, 3H), 1.32 (t, 3H, $J = 7.1$), 1.99 (dd, 1H, $^2J = 16.0$, $^4J = 1.0$), 2.07 (d, 1H, $^2J = 16.0$), 2.18 (d, 1H, $^2J = 16.8$), 2.33 (dd, 1H, $^2J = 16.8$, $^4J = 1.0$), 2.80–3.07 (m, 4H), 3.48–3.68 (m, 2H), 3.77–3.89 (m, 1H), 4.09–4.25 (m, 3H), 5.84 (s, 1H), 6.90–6.96 (m, 1H), 7.05–7.16 (m, 3H), 7.25–7.40 (m, 5H), 8.05 (br s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz, δ (ppm)): 14.8, 27.2, 29.1, 30.0, 31.1, 36.9, 39.3, 39.8, 45.1, 50.5, 51.7, 61.7, 109.5, 125.4, 125.5, 126.7, 128.5, 128.7, 128.9, 134.0, 137.9, 138.8, 157.0, 163.4, 192.9; **4k**: ^{1}H NMR ($CDCl_3$, 250 MHz, δ (ppm), J (Hz)): 0.97 (s, 3H), 0.99 (s, 3H), 1.26 (t, 3H, $J = 7.1$), 2.00 (dd, 1H, $^2J = 16.0$, $^4J = 1.0$), 2.09 (d, 1H, $^2J = 16.0$), 2.24 (d, 1H, $^2J = 17.0$), 2.42 (dd, 1H, $^2J = 17.0$, $^4J = 1.0$), 2.68–2.95 (m, 2H), 3.73 (s, 3H), 3.80–3.92 (m, 1H), 3.83 (s, 3H), 4.02–4.11 (m, 1H), 4.12 (q, 2H, $J = 7.1$), 4.52 (app d, 2H, $J = 6.3$), 5.88 (s, 1H), 6.45 (s, 1H), 6.58 (s, 1H), 7.25–7.39 (m, 5H), 8.37 (br s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz, δ (ppm)): 14.7, 26.9, 28.6, 29.9, 31.1, 39.5, 46.7, 50.5, 51.2, 55.6, 55.7, 61.7, 108.3, 110.5, 111.0, 125.8, 126.6, 127.4, 128.7, 129.3, 138.8, 146.8, 147.1, 157.0, 163.4, 193.4.

9. *Synthesis of compounds* **5**, *general procedure*: Compound **4** (0.25 mmol) was dissolved in THF (5 mL) and $NaNH_2$ (0.40 mmol, 16 mg) was added. The mixture was magnetically stirred and heated at reflux for 1.5 h. The solvent was then removed in vacuo and water (50 mL) was added. The product was extracted with dichloromethane (3 × 30 mL), the combined organic layers were dried (Na_2SO_4) and the solvent was removed by distillation. Trituration with Et_2O or filtration through a short silica column using Et_2O as eluent provided **5** as an analytically clean sample. *Representative NMR data* ($CDCl_3$, 600 MHz, δ (ppm), J (Hz)): **5d**: ^{1}H NMR: 0.87 (s, 3H), 1.04 (s, 3H), 2.01 (d, 1H, $^2J = 17.2$), 2.14 (d, 1H, $^2J = 17.2$), 2.26 (d, 1H, $^2J = 16.1$), 2.31 (d, 1H, $^2J = 16.1$), 2.68–2.83 (m, 3H), 3.25–3.31 (m, 2H), 3.64–3.69 (m, 1H), 4.08–4.13 (m, 1H), 4.45–4.51 (m, 1H), 5.61 (s, 1H), 6.80–7.21 (m, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): 26.00, 27.52, 32.03, 29.64, 35.97, 39.92, 44.14, 44.53, 49.44, 52.11, 108.83, 125.12, 126.06, 126.50, 127.09, 128.58, 129.08, 129.17, 134.50, 137.61, 138.12, 153.17, 153.80, 195.63; **5k**: ^{1}H NMR ($CDCl_3$, 600 MHz): 0.94 (s, 3H), 1.04 (s, 3H), 2.32–2.39 (m, 4H), 2.66–2.71 (m, 1H), 3.27–3.34 (m, 2H), 3.72 (s, 3H), 3.86 (s, 3H), 4.50–4.55 (m, 1H), 4.81 (d, 1H, $^2J = 16.2$), 5.14 (d, 1H, $^2J = 16.2$), 5.61 (s, 1H), 6.41 (s, 1H), 6.61 (s, 1H), 6.87–6.89 (m, 2H), 7.16–7.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): 26.38, 26.89, 29.60, 32.44, 39.81, 44.54, 46.06, 49.77, 52.03, 55.76, 55.92, 108.31, 110.55, 111.77, 125.57, 126.68, 127.20, 128.79, 129.65, 137.53, 147.08, 148.08, 154.13, 195.73.