ISSN 1070-4280, Russian Journal of Organic Chemistry, 2016, Vol. 52, No. 2, pp. 196–199. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © V.Yu. Kuksenok, V.V. Shtrykova, V.D. Filimonov, S.P. Sidel'nikova, 2016, published in Zhurnal Organicheskoi Khimii, 2016, Vol. 52, No. 2, pp. 214–216.

Efficient One-Stage Procedure of Beckmann Ketones Rearrangement in the Presence of Hydroxylamine

V. Yu. Kuksenok, V. V. Shtrykova, V. D. Filimonov, and S. P. Sidel'nikova

National Research Tomsk Polytechnic University, pr. Lenina 30, Tomsk, 634050 Russia
e-mail: vera.kuksenok@mail.ru

Received September 23, 2015

Abstract—Ketoximes formed from ketones in the presence of hydroxylamine and silica gel in formic acid undergo *in situ* the Beckmann rearrangement under mild conditions affording in high yields the corresponding amides. Unsymmetrical aromatic ketones, methyl aryl ketones, and methyl cyclohexyl ketone under these conditions form as a rule amides mixtures.

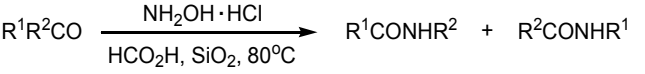
DOI: 10.1134/S1070428016020056

Beckmann rearrangement is an important method of synthesis of *N*-substituted amides from ketoximes that is widely utilized in the organic synthesis and in the synthesis of bioactive compounds [1]. As a rule, Beckmann rearrangement occurs at treating ketoximes with various protic and aprotic acid agents [1–3]. The rearrangement versions were described performed in ionic liquids [4], in vapor phase [5], and at microwave activation [6]. Notwithstanding the versatility of reagents in most cases the reaction proceeds in rather stringent conditions with the use of heavy metals compounds, corrosive hazardous and toxic substances.

Rare examples were published of Beckmann rearrangement performance where ketone and hydroxylamine were used as initial compounds, and the oxime rearrangement occurred *in situ* in the presence of trifluoroacetic acid [7, 8]. However at this procedure the incomplete conversion of ketones was observed. For instance, the benzophenone conversion was only 26% [8].

We found that the Beckmann rearrangement successfully occurred within 2.5 h at heating benzophenone **1** with hydroxylamine at 80°C in formic acid in the presence of silica gel resulting in a complete conversion of the initial ketone and nearly quantitative yield of benzanilide **11**. The optimum reagents ratio is as follows: 10 mmol of benzophenone, 30 mmol of $NH_2OH{\cdot}HCl$, 8 mL of HCO_2H, 1 g of silica gel.

Without silica gel the reaction takes 4 h and provides 80% yield of amide **11**. At replacing formic by acetic acid the reaction proceeds to a low conversion of benzophenone and the amide **11** yield not exceeding 10%. Amide **11** obtained by this procedure possesses the purity > 98% (according to the data of GC, HPLC, and NMR spectra) and does not require recrystallization or chromatographic purification unlike the products obtained by most known procedures of the Beckmann rearrangement. The accelerating effect of silica gel is apparently due to its dehydrating properties.



1–10 **11**, **12a–19a**, **20** **12b–17b**, **19b**

R^1 = Ph, R^2 = Ph (**1**, **11**), *o*-ClC_6H_4 (**2**, **12a**, **12b**), *m*-ClC_6H_4 (**3**, **13a**, **13b**), *p*-ClC_6H_4 (**4**, **14a**, **14b**), *m*-BrC_6H_4 (**5**, **15a**, **15b**), *p*-HOC_6H_4 (**6**, **16a**, **16b**); R^1 = Me, R^2 = Ph (**7**, **17a**, **17b**), *p*-$NO_2C_6H_4$ (**8**, **18a**), C_6H_{13} (**9**, **19a**, **19b**); $R^1 + R^2$ = C_5H_{10} (**10**, **20**).

The found optimal conditions were used in the investigation of the new version of Beckmann rearrangement on a series of aromatic and aliphatic ketones and on cyclohexanone (see the table).

As seen from the table, in the majority of cases the rearrangement of unsymmetrical ketones affords a mixture of two amides **12a**, **12b–17a**, **17b**, **19a**, and **19b**. The direction of Beckmann rearrangement of unsymmetrical ketoximes is governed mainly by their geometric structure: The group present in the *E*-position with respect to OH group of oxime migrates

to the nitrogen atom [1]. The ratio of the rearrangement products **a/b** in some cases corresponds to the isomeric composition of the intermediate ketoximes. According to [9], *o*-chlorobenzophenone formed *E*- and *Z*-oximes in the ratio 4 : 1, and the ratio of obtained rearrangement products of *o*-chlorobenzophenone **12a** and **12b** was 5.2 : 1 (see the table), sufficiently close to the ratio of *E*- and *Z*-isomers. It is also known that the rearrangement of acetophenone oximes $XC_6H_4C(NOH)Me$ furnishes mainly *N*-arylacetamides $XC_6H_4NHCOMe$ [2] in agreement with the prevailing formation of compounds **17a** and **18a**. The predominant formation of amide **19b** with the migration of a methyl group to the nitrogen atom corresponds to the greater stability of the *Z*-isomer of ketoxime $MeC(=NOH)C_6H_{13}$ [10]. Acetophenone oxime **7** that we prepared in standard conditions was according to HPLC data a mixture of *E*- and *Z*-isomers in the ratio 80 : 20, practically coinciding with the ratio of compounds **17a** and **17b**.

The rearrangement of *p*-chlorobenzophenone oxime under the action of $H_3PW_{12}O_{40}$ proceeds with the prevailing migration of the unsubstituted benzene ring with the formation of amide **14b** [3], in contrast to our result for we have obtained predominantly amide **14a**. Another example of difference between the isomers ratio **a/b** and *E/Z*-isomeric composition of oximes is the result of the rearrangement of *m*-chlorobenzophenone **3**, where the migration of the chlorobenzene ring furnished the minor product **13a** (10%) (see the table). Benzophenone **3** under standard conditions formed the oxime with practically equal amount of *E*- and *Z*-isomers (HPLC data). Evidently, the *E/Z*-isomeric composition of oximes formed in HCO_2H in the presence of SiO_2 differs from the oximes composition obtained under the standard conditions. However our attempts to isolate the intermediate oximes were unsuccessful since the oxime formation occurred simultaneously with their rearrangement.

Detailed understanding of the causes of the obtained selectivity requires a special investigation and is outside the scope of this study.

The structure of amides **11**, **12a**, **12b–17a**, **17b**, **18a**, **19a**, **19b**, and **20** and their ratio in the mixtures was established from the data of ^1H and ^{13}C, GC-MS, and HPLC in comparison with the spectral and chromatographic parameters of authentic compounds.

The developed one-stage procedure of Beckmann rearrangement of ketone under the action of hydroxylamine in formic acid with added silica gel as a dehydrating agent provides a possibility to perform the reaction under mild conditions, to obtain amides in high yields, and does not require applying toxic and hazardous components.

Results of Beckmann rearrangement of ketones **1–10** in the presence of hydroxylamine and silica gel in formic acid at 80°C

Ketone	Isomers ratio of amides **12–19**[a] (according to GC-MS data), %		Overall yield of amides **11–20**, %	Reaction time, h
	a	**b**		
1	–	–	98	2.5
2	84	16	85	5
3	10	90	97	3
4	63	37	87	3.5
5	29	71	90	4
6	91	9	92	4
7	77	23	95	3.5
8	100	–	90	4
9	25	75	82	5
10	–	–	79	4

[a] Compounds **11** and **20** cannot have isomers.

EXPERIMENTAL

^1H, ^{13}C NMR were registered on a spectrometer Bruker AC-300 in DMSO-d_6. GC-MS and HPLC procedures were carried out on instruments Agilent 7890/5975C (chromatographic column HP-5MS 30 m × 250 μm × 0.25 μm) and Agilent 1200 (stainless steel chromatographic column 150 × 4.6 mm packed with adsorbent Zorbax Extend, C-18, particle size 5 μm). Conditions of GC-MS analysis: ramp from 40 to 290°C at a rate 10 deg/min, isothermal at 290°C for 15 min. Input volume 1 μL, split ratio 50 : 1. Vaporizer temperature 290°C. Conditions of HPLC analysis: mobile phase acetonitrile–water (gradient elution from 100% of water till 100% of acetonitrile to the end of analysis), flow rate of the mobile phase 1.0 mL/min, analysis time 10 min, detection at λ 230 nm. Melting points were measured on an instrument MP50 (Mettler Toledo).

Initial ketones of reagent purity were used without additional purification. Silica gel was purchased from Aldrich, particle size 40–63 μm, pore diameter 60 Å, before use silica gel was calcined for 30 min at 250°C. The identification of amide mixtures **12a**, **12b–17a**,

17b, **19a**, and **19b** and estimation of their ratio was performed by GC-MS and HPLC methods applying the addition of standard compounds. The following retention times were established (min), GC: **12a** 22.0, **12b** 22.4, **13a** 21.1, **13b** 21.4, **14a** 20.6, **14b** 20.4, **15a** 21.3, **15b** 21.5, **16a** 23.0, **16b** 23.4, **17a** 13.9, **17b** 9.3, **18a** 16.3, **19a** 10.4, **19b** 9.0; HPLC: **12a** 7.5, **12b** 7.2, **13a** 8.3, **13b** 8.0, **14a** 7.7, **14b** 8.3, **15a** 7.8, **15b** 7.5, **16a** 23.0, **16b** 23.4, **17a** 4.9, **17b** 6.1, **18a** 6.4, **19a** 7.5, **19b** 7.2.

Amides 11–20. General procedure. A mixture of 10 mmol of ketone **1–10**, 30 mmol of hydroxylamine hydrochloride, 1 g of silica gel in 8 mL of formic acid was heated at 80°C while stirring (TLC monitoring) for the time indicated in the table. Silica gel was filtered from the reaction mixture, the filtrate was diluted with 150 mL of water and neutralized with 20% solution of NaOH. The separated precipitate of amides **11**, **12a**, **12b–16a**, **16b**, and **18a** was filtered off, washed with water on the filter, and dried. Amides **17a**, **17b**, **19a**, **19b**, and **20** were extracted from the water solution with toluene (3 × 20 mL), the extract was dried with Na_2SO_4 and evaporated on a rotary evaporator.

The prevailing amide isomer obtained from ketones **2–6** was isolated by recrystallization from 2-propanol. Amides **17a**, **17b** and **19a**, **19b** were analyzed as mixtures.

Benzanilide (11). Yield 98%, mp 162–163°C. ^{1}H NMR spectrum, δ, ppm: 7.08–7.13 t (1H), 7.33–7.39 t (2H), 7.51–7.61 m (3H), 7.79–7.82 d (2H), 7.96–7.99 d (2H), 10.28 s (1H). ^{13}C NMR spectrum, δ, ppm: 120.24, 123.54, 127.51, 128.27, 128.48, 131.43, 134.85, 139.02, 165.39.

***N*-(2-Chlorophenyl)benzamide (12a).** Yield 57%, mp 103–104°C. ^{1}H NMR spectrum, δ, ppm: 7.05–7.09 m (1H), 7.31–7.33 t (1H), 7.40–7.42 d (1H), 7.49–7.52 m (2H), 7.56–7.59 t (1H), 7.89–7.92 d (2H), 8.43 s (1H), 8.56–8.58 d (1H).

***N*-Phenyl-3-chlorobenzamide (13b).** Yield 85%, mp 136–137°C. ^{1}H NMR spectrum, δ, ppm: 7.09–7.14 t (1H), 7.34–7.39 t (2H), 7.54–7.59 t (1H), 7.65–7.68 d (1H), 7.75–7.68 d (2H), 7.90–7.92 d (1H), 8.01 s (1H). ^{13}C NMR spectrum, δ, ppm: 120.37, 123.79, 126.40, 127.35, 128.57, 130.34, 131.36, 133.18, 136.89, 138.79, 163.71.

***N*-(4-Chlorophenyl)benzamide (14a).** Yield 53%, mp 187–189°C. ^{1}H NMR spectrum, δ, ppm: 7.09–7.13 t (1H), 7.34–7.42 d (2H), 7.52–7.62 d (2H), 7.75–7.93 d (2H), 7.95–7.99 t (2H), 10.30 s (1H).

***N*-Phenyl-3-bromobenzamide (15b).** Yield 62%, mp 141–142°C. ^{1}H NMR spectrum, δ, ppm: 7.10–7.13 t (1H), 7.35–7.38 t (2H), 7.50–7.52 d (2H), 7.76–7.78 d (2H), 7.94–7.97 t (2H), 8.13 s (1H), 10.34 s (1H).

***N*-(4-Hydroxyphenyl)benzamide (16a).** Yield 80%, mp 209–211°C. ^{1}H NMR spectrum, δ, ppm: 6.73–6.76 d (2H), 7.52–7.54 m (5H), 7.91–7.93 d (2H), 9.25 s (1H). ^{13}C NMR spectrum, δ, ppm: 114.93, 122.24, 127.46, 128.30, 130.65, 131.25, 135.14, 153.67, 164.83.

***N*-Phenylacetamide (17a).** Mass spectrum: *m/z* 135 $[M]^+$, 93, 66, 63, 43.

***N*-Methylbenzamide (17b).** Mass spectrum: *m/z* 135 $[M]^+$, 105, 77, 51.

***N*-(4-Nitrophenyl)acetamide (18a).** Yield 90%, mp 216–218°C. ^{1}H NMR spectrum, δ, ppm: 3.37 s (3H), 7.93–7.95 d (2H), 8.25–8.27 d (2H), 11.80 s (1H).

***N*-Cyclohexylacetamide (19a).** Mass spectrum: *m/z* 141 $[M]^+$, 111, 97, 79, 69, 60, 54.

***N*-Methylcyclohexanecarboxamide (19b).** Mass spectrum: *m/z* 141 $[M]^+$, 126, 112, 98, 84, 70, 56, 43, 28.

Hexahydro-2*H*-azepin-2-one (20). Yield 79%, mp 68–70°C. ^{1}H NMR spectrum, δ, ppm: 1.71–1.76 m (6H), 2.40–2.45 m (2H), 3.14–3.24 m (2H), 6.49 br (1H).

The study was carried out under the financial support of the State contract “Nauka” (project no. 2387).

REFERENCES

1. Smith, M.B. and March, J., *Advanced Organic Chemistry*, 5th Ed., New York: John Wiley & Sons, 2001.
2. Augustine, J.K., Kumar, R., Bombrun, A., and Mandal, A.B., *Tetrahedron Lett*., 2011, vol. 52, p. 1074.
3. Kaur, G., Rajput, J.K., Arora, P., and Devi, N., *Tetrahedron Lett*., 2014, vol. 55, p. 1136.
4. Maia, A., Albanese, D.C.M., and Landini, D., *Tetrahedron*, 2012, vol. 68, p. 1947.

5. Anilkumar, M. and Hoelderich, W.F., *Catal. Today*, 2012, vol. 198, p. 289.
6. Sridhar, M., Narsaiah, C., Sairam, V.V., Reddy, G.K., Raveendra, J., Reddy, M.K.K., and Ramanaiah, B.C., *Tetrahedron Lett*., 2011, vol. 51, p. 6103.
7. Rad, M.N.S., Khalafi-Nezhad, A., Behrouz, S., Amini, Z., and Behrouz, M., *Phosph., Sulfur, Silicon*, 2010, vol. 185, p. 1658.
8. Aricò, F., Quartarone, G., Rancan, E., Ronchin, L., Tundo, P., and Vavasori, A., *Catal. Commun*., 2014, vol. 49, p. 47.
9. Inamoto, K., Katsuno, M., Yoshino, T., Arai, Y., Hiroya, K., and Sakamoto, T., *Tetrahedron*, 2007, vol. 63, p. 2695.
10. Beauchemin, A.M., Moran, J., Lebrun, M.-E., Seguin, C., Dimitrijevic, E., Zhang, L., and Gorelsky, S.I., *Angew. Chem., Int. Ed*., 2008, vol. 47, p. 1410.