



Tetrahedron Letters 44 (2003) 3027-3030

TETRAHEDRON LETTERS

First radical addition onto ketenimines: a novel synthesis of indoles

Mateo Alajarin, Angel Vidal* and Maria-Mar Ortin

Departamento de Quimica Organica, Facultad de Quimica, Universidad de Murcia, Campus de Espinardo, Espinardo 30071, Murcia, Spain

Received 18 February 2003; accepted 27 February 2003

Abstract—A novel radical-mediated synthesis of 2-alkyl indoles is described. The method is a nonchain process based on the intramolecular addition of benzylic radicals onto the central carbon atom of a ketenimine function, resulting in a 5-exo-dig cyclization. \bigcirc 2003 Elsevier Science Ltd. All rights reserved.

The intramolecular cyclization by addition of carbon centered free-radicals to carbon–carbon or carbon–heteroatom multiple bonds has become a very useful and standard strategy for the construction of complex carbocyclic and heterocyclic compounds, in the growing field of the modern synthetic radical chemistry.¹

Over the past several years, we have been involved in the study of the reactivity of ketenimines. In our hands, these heterocumulenes were particularly useful in the synthesis of nitrogen-containing heterocycles through their participation in electrocyclic ring closures,² intramolecular $[2+2]^3$ and $[4+2]^4$ cycloadditions, and imino-ene type reactions.⁵ We have now focused our attention on the development of radical processes involving ketenimines as substrates. To the best of our knowledge, no inter- or intramolecular free radical addition to ketenimines has been reported. Moreover, the free radical chemistry of heterocumulenes is practically unknown,⁶ with the exception of that of ketenes which is being currently investigated by Tidwell.⁷

We present here the intramolecular addition of benzylic radicals, generated from xanthates, onto a ketenimine function with its N atom linked to the *ortho* position of the aromatic ring. These radical cyclizations represent a new protocol for the synthesis of indoles.⁸

Amongst all the common functionalities for producing carbon-centered radicals we selected the xanthate group. In the last few years Zard has nicely shown that xanthates behave as clean and efficient sources of carbon radicals.⁹ Furthermore, the xanthate group is compatible with our methodology for the preparation of ketenimines, via aza-Wittig reaction of phosphazenes and ketenes,^{2–5} and ketenimines should not be altered under the reaction conditions generally applied to convert xanthates into radicals.

Ketenimines 4 were specifically designed for generating benzylic radicals which could undergo intramolecular 5-exo-dig cyclization onto the central carbon atom of the ketenimine function. The presence of phenyl groups at the terminal carbon atom of the ketenimine is aimed to favor the cyclization by conferring stability to the resulting radicals. Compounds 4 were readily obtained in high overall yields from 2-azidobenzylbromides or chlorides 1^{10} in three steps, namely by (i) substitution of the bromine or chlorine atom by the xanthate group using the commercially available xanthate salt KSC(S)OEt, (ii) reaction of the azide function in xanthates 2 with triphenylphosphane and (iii) treatment of the resulting triphenylphosphazenes 3 with methyl phenyl ketene or diphenyl ketene (Scheme 1).

Radical cyclization of ketenimines **4** was explored under different conditions. The addition, in small portions, of a stoichiometric amount of benzoyl peroxide as radical initiator to a solution of ketenimine **4c** (0.01 M) in boiling benzene did not proceed at all leaving **4c** unaltered. However, the reaction initiated by lauroyl peroxide and conducted in refluxing cyclohexane pro-

Keywords: cyclization; indoles; ketenimines; radical reactions.

^{*} Corresponding author. Tel.: +34 968 367418; fax: +34 968 364149; e-mail: vidal@um.es

^{0040-4039/03/\$ -} see front matter @ 2003 Elsevier Science Ltd. All rights reserved. doi:10.1016/S0040-4039(03)00562-8

duced the indole 6a, which incorporated the lauroyloxy fragment, in 38% yield, along with a small amount (4%)of the reduced indole **5c**. The 2-(methoxydiphenyl)methylindole **6b** ($R^5 = CH_3$) was obtained in 43% yield when lauroyl peroxide was used as initiator and a mixture of methanol/1,2-dichloroethane (1:3; v/v)as solvent.¹¹ When a stoichiometric amount of t-butyl peroxide was portionwise added to a solution of compound 4c (0.01 M) in boiling chlorobenzene 5-chloro-2diphenylmethylindole 5c was obtained in 60% yield, as the only product which could be isolated. Cyclization of ketenimines 4a,b,d-h under the same reaction conditions furnished further examples of 2-substituted indoles 5 in moderate yields (Table 1).¹²

A reasonable mechanism for explaining the conversions $4 \rightarrow 5/6$ is shown in Scheme 2. The thermal decomposi-



Scheme 1. Reagents and conditions: (i) KSC(S)OEt, acetone, rt, 1 h; (ii) PPh₃, diethyl ether, rt, 6 h; (iii) PhR⁴C=C=O, dichloromethane, rt, 30 min; (iv) lauroyl peroxide (1.5 equiv.), cyclohexane, reflux, 30 h, to give **6a**; (v) lauroyl peroxide (1.2 equiv.), methanol/1,2-dichloroethane, reflux, 24 h, to give **6b**; (vi) *t*-butyl peroxide (1.2 equiv.), chlorobenzene, reflux, 24 h.

Table 1. 2-Substituted indoles 5 from ketenimines 4

Compd	\mathbb{R}^1	R ²	R ³	\mathbb{R}^4	Yield (%)	
5a	Н	Н	Н	Ph	50	
5b	Br	Н	Н	Ph	24	
5c	Cl	Н	Н	Ph	60	
5d	CH ₃	Н	Н	Ph	47	
5e	Н	NO_2	Н	Ph	64	
5f	Н	Н	CH_3	Ph	60	
5g	(C_6H_4		Ph	52	
5h	Н	Н	Н	CH_3	44	



Scheme 2. Proposed mechanism for the conversions $4 \rightarrow 5/6$.

tion of the peroxide initiator produces radical $(R_0)^{\bullet}$, which exchanges the xanthate group with ketenimines 4 giving rise to the expected benzylic radicals 12. The intermediate species 12 undergo a 5-*exo* addition of the radical moiety onto the central carbon of the ketenimine function, followed by a prototropic imine–enamine equilibrium favoring the indole form 14. The stabilized tertiary radicals 14 did not react with a new molecule of 4 to sustain the radical chain sequence.¹³ Instead they underwent reduction to give indoles 5, or electron transfer to the lauroyl peroxide to furnish

carbocations 15, which finally were quenched by the carboxylate anion generated in the redox process (to furnish 6a)¹⁴ or the methanol used as solvent (to furnish 6b).^{14b}

The conversion $4\rightarrow 5$ is a reductive process and the source of the hydrogen atom that quenched the radical 14 is not obvious.¹⁵ We reasoned that the yield of the reaction might be improved by addition to the reaction mixture of hydrogen donors, but many of them are incompatible with the ketenimine function. Addition of 1,4-cyclohexadiene to one of the initial reaction mixtures led to a cleaner reaction, but the yield of the corresponding indole 5 did not improve.

Attempts of trapping intermolecularly the benzylic radical **12** by carrying out the radical cyclization of ketenimines **4** in the presence of an excess of allyl acetate or benzyl acrylate failed, proving that the intramolecular cyclization is a more favorable path due to the great stability of the triarylmethyl-type radicals **13** and **14**.

In conclusion, we have shown how ketenimines react with free carbon-centered radicals in an intramolecular process providing a new radical tin-free route to indoles. Extension of this radical cyclization onto ketenimines to a variety of carbon- and nitrogen-centered radicals is currently under investigation.

Acknowledgements

This work was supported by the MCYT and FEDER (Project BQU2001-0010), and Fundacion Seneca-CARM (Project PI-1/00749/FS/01). One of us (M.-M. O.) thanks the Fundacion Seneca-CARM for a fellowship.

References

- (a) Giese, B. Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds; Pergamon: Oxford, 1988; (b) Curran, D. P. In Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p. 715; (c) Motherwell, W. B.; Crich, D. In Free Radical Chain Reactions in Organic Synthesis; Academic Press: London, 1992; (d) Leffler, J. E. In An Introduction to Free Radicals; Wiley-Interscience: New York, 1993; (e) Fossey, J.; Lefort, D.; Sorba, J. In Free Radicals in Organic Chemistry; John Wiley and Sons: Chichester, 1995; (f) Curran, D. P.; Porter, N. A.; Giese, B. In Stereochemistry of Radical Reactions; VCH: Weinheim, 1995; (g) Radicals in Organic Synthesis; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.
- (a) Molina, P.; Alajarin, M.; Vidal, A.; Fenau-Dupont, J.; Declerq, J. P. J. Org. Chem. 1991, 56, 4008–4016; (b) Molina, P.; Alajarin, M.; Vidal, A.; Foces-Foces, C. *Tetrahedron* 1995, 51, 12127–12142; (c) Molina, P.; Vidal, A.; Barquero, I. Synthesis 1996, 1199–1202; (d) Molina, P.; Vidal, A.; Tovar, F. Synthesis 1997, 963–966.
- 3. (a) Alajarin, M.; Molina, P.; Vidal, A. Tetrahedron Lett.

1996, *37*, 8945–8948; (b) Alajarin, M.; Molina, P.; Vidal, A.; Tovar, F. *Tetrahedron* **1997**, *53*, 13449–13472; (c) Alajarin, M.; Vidal, A.; Tovar, F.; Arrieta, A.; Lecea, B.; Cossio, F. P. *Chem. Eur. J.* **1999**, *5*, 1106–1117; (d) Cossio, F. P.; Arrieta, A.; Lecea, B.; Alajarin, M.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2000**, *65*, 3633–3643; (e) Alajarin, M.; Vidal, A.; Tovar, F.; Ramirez de Arellano, M. C.; Cossio, F. P.; Arrieta, A.; Lecea, B. *J. Org. Chem.* **2000**, *65*, 7512–7515.

- (a) Alajarin, M.; Vidal, A.; Tovar, F.; Conesa, C. *Tetrahedron Lett.* **1999**, 40, 6127–6130; (b) Alajarin, M.; Vidal, A.; Tovar, F. *Tetrahedron Lett.* **2000**, 41, 7029–7032; (c) Alajarin, M.; Vidal, A.; Ortin, M.-M. *Synthesis* **2002**, 2393–2398.
- 5. Alajarin, M.; Vidal, A.; Tovar, F.; Sanchez-Andrada, P. *Tetrahedron Lett.* 2002, 43, 6259–6261.
- To our knowledge no examples of radical reactions involving carbodiimides or isocyanates have been reported. For examples of radical addition to isothiocyanates, see: (a) Barton, D. H. R.; Jaszberenyi, J. Cs.; Theodorakis, E. A. *Tetrahedron* 1992, 48, 2613–2626; (b) Bachi, M. D.; Denenmark, D. J. Org. Chem. 1990, 55, 3442–3444; (c) Bachi, M. D.; Bar-Ner, N.; Melman, A. J. Org. Chem. 1996, 61, 7116–7124; (d) Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. J. Org. Chem. 2000, 65, 8669–8674.
- (a) Sung, K.; Tidwell, T. T. J. Org. Chem. 1998, 63, 9690–9697; (b) Allen, A. D.; Cheng, B.; Fenwick, M. H.; Huang, W.; Missiha, S.; Tahmassebi, D.; Tidwell, T. T. Org. Lett. 1999, 1, 693–696; (c) Huang, W.; Henry-Riyad, H.; Tidwell, T. T. J. Am. Chem. Soc. 1999, 121, 3939– 3943; (d) Allen, A. D.; Cheng, B.; Fenwick, M. H.; Givehchi, B.; Henry-Riyad, H.; Nikolaev, V. A.; Shikhova, E. A.; Tahmassebi, D.; Tidwell, T. T.; Wang, S. J. Org. Chem. 2001, 66, 2611–2617; (e) Allen, A. D.; Fenwick, M. H.; Henry-Riyad, H.; Tidwell, T. T. J. Org. Chem. 2001, 66, 5759–5765; (f) Allen, A. D.; Porter, J.; Tahmassebi, D.; Tidwell, T. T. J. Org. Chem. 2001, 66, 7420–7426; (g) Tidwell, T. T.; Fenwick, M. H. Eur. J. Org. Chem. 2001, 3415–3419.
- For radical cyclizations leading to indoles, see: (a) Gribble, G. W. Contemp. Org. Synth. 1994, 1, 145–172; (b) Gribble, G. W. J. Chem. Soc., Perkin Trans. 1 2000, 1045–1075; (c) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. J. Am. Chem. Soc. 1999, 121, 3791–3792; (d) Reding, M. T.; Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. Heterocycles 2002, 56, 313–330; (e) Murphy, J. A.; Scott, K. A.; Sinclair, R. S.; Lewis, N. Tetrahedron Lett. 1997, 38, 7295–7298; (f) Montevecchi, P. C.; Navacchia, M. L. Tetrahedron Lett. 1998, 39, 9077–9080; (g) Rainier, J. D.; Kennedy, A. R.; Chase, E. Tetrahedron Lett. 1999, 40, 6325–6327.
- For reviews on the radical xanthate transfer reaction, see:
 (a) Zard, S. Z. reference 1g, pp. 90–108; (b) Zard, S. Z. Angew. Chem., Int. Ed. Engl. 1997, 36, 672–685; (c) Quiclet-Sire, B.; Zard, S. Z. Phosphorus, Sulfur Silicon 1999, 153–154, 137–154.
- 2-Azidobenzylbromides and chlorides 1 have been prepared following general experimental procedures previously described: (a) Molina, P.; Alajarin, M.; Vidal, A. J. Org. Chem. 1993, 58, 1687–1695; (b) Alajarin, M.; Lopez-Lazaro, A.; Vidal, A.; Berna, J. Chem. Eur. J. 1998, 4, 2558–2570.

- 11. A small amount (17%) of the imidate resulting from the addition of methanol to the central carbon atom of the cumulene function in ketenimine **4c** was also isolated in this reaction.
- 12. (a) 2-Diphenylmethylindole 5a is a known compound: Dolby, L. L. J.; Lord, P. D. J. Org. Chem. 1969, 34, 2988-2993; (b) Satisfactory ¹H and ¹³C NMR, mass spectra and elemental analyses were obtained for all new compounds. (c) Typical procedure: a solution of the corresponding ketenimine xanthate 4 (0.6 mmol) in anhydrous chlorobenzene (60 ml) was heated under nitrogen to reflux and t-butyl peroxide added (0.10 g, 0.72 mmol) portionwise (0.12 mmol every 4 h). After 4 h since the last addition the solvent was removed under reduced pressure and the crude residue was purified by silica gel column chromatography (hexanes/diethyl ether 9:1). After removing the solvent from the column chromatography under reduced pressure the resulting solid material was triturated, dried at room temperature under high vacuum for 12 h, and used as such for characterization. Compounds 5 were stored under nitrogen atmosphere to avoid air oxidation.

5-Chloro-2-diphenylmethylindole (5c): yield 60%; IR (Nujol) 3417, 1600, 1575, 1309, 1218, 1137, 1061, 919,

867, 796, 748, 701 cm⁻¹; ¹H NMR (CDCl₃) δ 5.50 (s, 1H), 6.00 (d, 1H, J=1.2 Hz), 7.03 (d, 2H, J=1.2 Hz), 7.14– 7.34 (m, 10H), 7.42 (s, 1H), 7.74 (br s, 1H); ¹³C NMR (CDCl₃) δ 51.0, 102.5, 111.6, 119.6, 121.8, 125.3 (s), 127.1, 128.7, 129.0, 129.4 (s), 134.5 (s), 141.8 (s), 142.4 (s). Mass spectrum m/z (relative intensity) 319 (M⁺+2, 20), 317 (M⁺, 82), 240 (100). Anal. calcd for C₂₁H₁₆ClN: C, 79.36; H, 5.07; N, 4.41. Found: C, 79.12; H, 4.98; N, 4.23.

- 13. This is the reason why the formation of 5/6 requires stoichiometric quantities of peroxide.
- (a) Coppa, F.; Fontana, F.; Minisci, F.; Pianese, G.; Tortoreto, P.; Zhao, L. *Tetrahedron Lett.* **1992**, *33*, 687– 690; (b) Gagosz, F.; Moutrille, C.; Zard, S. Z. Org. Lett. **2002**, *4*, 2707–2709.
- For radical xanthate reaction transfers in which small amounts of reduced side products are obtained, see: (a) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. Angew. Chem., Int. Ed. Engl. 2000, 39, 731–733; (b) Kaoudi, T.; Miranda, L. D.; Zard, S. Z. Org. Lett. 2001, 3, 3125–3127. For similar reactions in which cyclohexane acts as an effective hydrogen atom donor, see: (c) Quiclet-Sire, B.; Zard, S. Z. J. Am. Chem. Soc. 1996, 118, 9190–9191.