Stereoselective Intra- and Intermolecular [2+2] Photocycloaddition Reactions of 4-(2′-Aminoethyl)quinolones

Sebastian Brandes, Philipp Selig, Thorsten Bach*

Lehrstuhl für Organische Chemie I, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany
Fax +49(89)28913315; E-mail: thorsten.bach@ch.tum.de

Received 20 July 2004

Abstract: The 4-(2′-aminoethyl)quinolones **6**, **8** and **9** were prepared starting from 4-(2′-bromoethyl)quinolone (**4**) in two steps and overall yields of 56–93%. They underwent inter- and intramolecular [2+2] photocycloaddition reactions with an alkene to provide the cyclobutanes **1**–**3** in racemic form (61–89% yield). The photochemical reaction proceeded with very good chemo-, regio- and stereoselectivity. It was in one case (**8b** → **2b**) also performed enantioselectively (93% ee).

Key words: asymmetric synthesis, cycloadditions, cyclobutanes, diastereoselectivity, photochemistry, quinolones

One of the hallmarks of organic photochemistry is the ease with which strained cyclobutanes can be prepared by [2+2] photocycloaddition reactions.[1] Consecutive transformations allow for the conversion of the cyclobutane ring into acyclic carbon substituents by ring-opening, or into other rings by rearrangement reactions.[2] In the course of a study directed towards the rearrangement of 3-azabicyclo[4.2.0]octanes into 2-azabicyclo[3.3.0]octanes, we required stereoselective access to compounds **1**–**3** (Figure 1). An apparent synthetic pathway involves the intra- or intermolecular [2+2] photocycloaddition reactions of 4-(2′-aminoethyl)quinolones which in turn appeared to be accessible from 4-(2′-bromoethyl)quinolone (**4**).[3] In this communication we report on our preliminary results in this field. We could show that the desired reaction was feasible with excellent chemo-, regio- and stereoselectivity. An enantioselective protocol was employed to provide cyclobutane **2b** in high enantiomeric excess (93% ee).

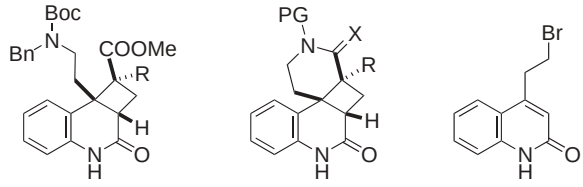
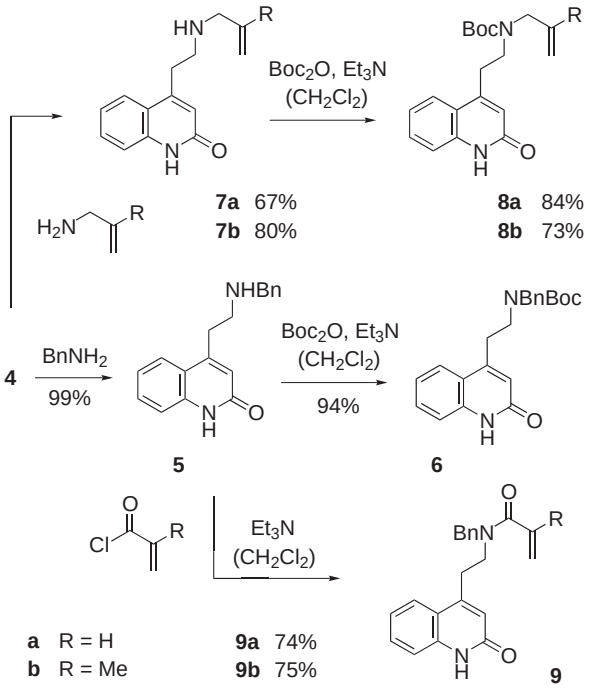


Figure 1 Structures of the cyclobutane targets **1**–**3** and of the readily available starting material **4**

The [2+2] photocycloaddition of the parent 2-quinolone (carbostyril) has been intensively studied.[4] Due to the high intersystem crossing rate a triplet pathway is followed which involves 1,4-biradical intermediates.[4f] Simple 4-alkyl-2-quinolones have also been used in intermolecular photocycloaddition reactions.[4c,d,5] More complex 4-alkyl-2-quinolones, however, have not yet been employed nor have, to the best of our knowledge, intramolecular [2+2] photocycloaddition reactions of 4-alkyl-2-quinolones been studied.[6] Our own work commenced with the synthesis of potential precursors for the photocycloaddition. The starting material **4** was prepared from commercially available 4-methyl-2-quinolone by a sequence of carboxylation,[3a,b] esterification,[3c] reduction,[3c] and Appel bromination (60% overall). In order to get our hands at least on one of the three compounds **1**–**3** all possible routes were pursued in a parallel direction (Scheme 1). The parent *N*-benzyl(Bn)-*N*-*tert*-butyloxycarbonyl(Boc)-4-(2′-aminoethyl)quinolone (**6**), which is the precursor for an intermolecular [2+2] photocycloaddition, was obtained by treatment of bromide **4** with neat *N*-benzylamine and by subsequent acylation of amine **5** with Boc_2O. In an analogous fashion the *N*-allyl derivatives **8** were synthesized via the secondary *N*-allylamines **7**. The acrylamides **9** were obtained from amine **5** by acylation with acryloyl chloride and methacryloyl chloride, respectively.

Irradiation experiments were conducted in toluene solution at room temperature using a conventional merry-go-round apparatus (Duran filter).[7] Based on previous work[4–6] the successful intramolecular [2+2] photocycloadditon of substrates **8** was least surprising (Table 1, entries 3, 4). The most remarkable aspect concerns the ease with which the two quaternary stereogenic centers are formed in cyclobutane *rac*-**2b**. The regioselectivity is determined by the preferred formation of six-membered rings and the stereochemistry is a result of a preferred annulation to the cyclobutane in a *cis*-fashion. Cycloadditions of acrylates are less common than reactions of electron-rich alkenes with photoexcited α,β-unsaturated carbonyl compounds.[1] In this respect, the smooth photocycloaddition of methyl acrylate (entry 1) and even more importantly of methyl methacrylate (entry 2) to quinolone **6** came as a pleasant surprise. Attempted reactions at 300 nm (Rayonet RPR-3000 Å lamps) were sluggish but the reactions proceeded smoothly at 350 nm (RPR-3500 Å). Yields increased at higher concentration (30 mM vs. 5 mM) without any detectable quinolone dimerization. In a

SYNLETT 2004, No. 14, pp 2588–2590
Advanced online publication: 20.10.2004
DOI: 10.1055/s-2004-834817; Art ID: G27604ST



Scheme 1 Preparation of various 4-(2′-aminoethyl)quinolones **6**, **8**, and **9** from 4-(2′-bromoethyl)quinolone (**4**)

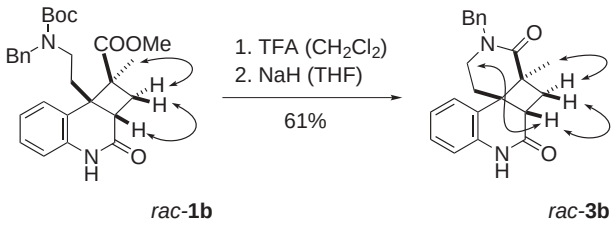
similar fashion the acrylamides **9** gave cyclobutanes *rac*-**3** in an intramolecular reaction (entries 5, 6). Quinolone **9a** was not soluble in toluene and the reaction was therefore conducted in a suspension.

If a triplet pathway is assumed for the [2+2] photocycloaddition,[1] the regioselectivity of the intermolecular reactions (entries 1, 2) can be accounted for by the formation of the most stable 1,4-biradical. The relative configuration of products *rac*-**1a** and *rac*-**1b** was unambiguously proven by ^{1}H NMR NOESY experiments. Moreover, compounds *rac*-**1a** and *rac*-**1b** could be readily converted into the tetracyclic products *rac*-**3a** and *rac*-**3b** upon *N*-Boc deprotection (Scheme 2, TFA = trifluoracetic acid). This transformation is only possible if the methoxycarbonyl group in cyclobutanes *rac*-**1a** and *rac*-**1b** is located *cis* to the corresponding N-protected 2-aminoethyl substituent. The transformation *rac*-**1a** → *rac*-**3a** proceeded simply after deprotection by heating the crude *N*-benzylamine in toluene for 1 hour under reflux (90% yield).

Table 1 Inter- (Entries 1, 2) and Intramolecular (Entries 3–6) Photocycloaddition of the Quinolones **6**, **8** and **9** in Toluene as the Solvent (Duran Filter)[7]

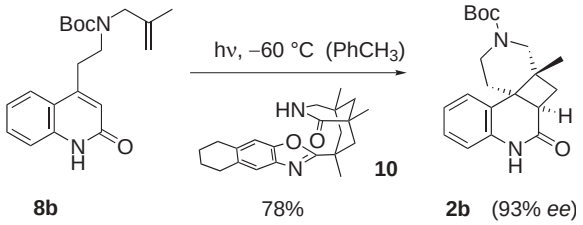
Entry	Substrate	λ (nm)	Product	Yield (%)[a]	dr[b]
1	**6**[c]	350	*rac*-**1a**	80	>95:5
2	**6**[d]	350	*rac*-**1b**	89	75:25
3	**8a**	300	*rac*-**2a**	85	>95:5
4	**8b**	300	*rac*-**2b**	84	>95:5
5	**9a**[e]	350	*rac*-**3a**	65	>95:5
6	**9b**	350	*rac*-**3b**	61	>95:5

[a] Yield of isolated product.
[b] The diastereomeric ratio (dr) was determined by integration of appropriate ^{1}H NMR signals from the crude product.
[c] The reaction was conducted in the presence of an excess (20 equiv) of methyl acrylate.
[d] The reaction was conducted in the presence of an excess (20 equiv) of methyl methacrylate.
[e] A suspension of compound **9a** was irradiated in toluene.



Scheme 2 Strong ^{1}H NOESY contacts recorded for compound *rac*-**1b** and for compound *rac*-**3b**, which could be obtained by intramolecular lactam formation from *rac*-**1b**

The presence of a lactam moiety in 2-quinolones allowed for the [2+2] photocycloaddition to be conducted in an enantioselective fashion (Scheme 3).[8] Employing the chiral complexing reagent **10**[9] (2.3 equiv), the reaction of **8b** → **2b** proceeded with excellent enantiomeric excess (93% ee). Toluene was used as the solvent at low temperature to facilitate association of the quinolone to lactam **10** by hydrogen bonds.[10] The photocycloaddition was performed using a high pressure mercury lamp (TQ 150, Duran filter).[11]



Scheme 3 Enantioselective intramolecular [2+2] photocycloaddition of substrate **8b** in the presence of the chiral complexing agent **10**

In summary, the intra- and intermolecular [2+2] photocycloaddition of the title compounds gave access to the tri- or tetracyclic products **1**–**3** in good to excellent chemical yields. The reaction proceeded with high regioselectivity and in all but one case with excellent simple diastereoselectivity. Three stereogenic centers were formed in one step, the absolute configuration of which can be controlled in an enantioselective variant of the reaction. The potential of complexing reagent **10** to achieve an efficient face differentation was shown for one example (**8b** → **2b**).

Further work directed towards an enantioselective approach to compounds **1**–**3** continues, as does research directed towards possible rearrangement and ring-opening reactions of these compounds.

Acknowledgment

This work was supported by the 2001 AstraZeneca research award to T. B. and by an AstraZeneca research assistantship to S. B. We are grateful to Dr. Kevin Foote (AstraZeneca, Alderley Park, UK) for many fruitful discussions and for his help throughout the course of this project.

References

(1) Reviews: (a) Fleming, S. A.; Bradford, C. L.; Gao, J. J. In *Molecular and Supramolecular Photochemistry: Organic Photochemistry*, Vol. 1; Ramamurthy, V.; Schanze, K. S., Eds.; Dekker: New York, **1997**, 187. (b) Bach, T. *Synthesis* **1998**, 683. (c) Pete, J.-P. *Adv. Photochem.* **1996**, *21*, 135. (d) Mattay, J.; Conrads, R.; Hoffmann, R. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed., Vol. E 21c; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, **1995**, 3085. (e) Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297. (f) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453. (g) Baldwin, S. W. *Org. Photochem.* **1981**, *5*, 123.

(2) Reviews: (a) Wong, H. N. C.; Fitjer, L.; Heuschmann, M. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed., Vol. E 17e; de Meijere, A., Ed.; Thieme: Stuttgart, **1997**, 435. (b) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.

(3) (a) Wolfe, J. F.; Trimitsis, G. B.; Morris, D. R. *J. Org. Chem.* **1969**, *34*, 3263. (b) Martin, O.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **1995**, *51*, 7547. (c) Uchida, M.; Tabusa, F.; Komatsu, M.; Morita, S.; Kanabe, T.; Nakagawa, K. *Chem. Pharm. Bull.* **1985**, *33*, 3775.

(4) The formation of photodimer was also observed. The simple diastereoselectivity in the [2+2] photocycloaddition of monosubstituted alkenes was low: (a) Evanega, G. R.; Fabiny, D. L. *J. Org. Chem.* **1970**, *35*, 1757. (b) Cantrell, T. S. *J. Org. Chem.* **1974**, *39*, 3063. (c) Buchardt, O.; Christensen, J. J.; Harrit, N. *Acta Chem. Scand. B* **1976**, *30*, 189. (d) Chiba, T.; Kato, T.; Yoshida, A.; Moroi, R.; Shimomura, N.; Momose, Y.; Naito, T.; Kaneko, C. *Chem. Pharm. Bull.* **1984**, *32*, 4707. (e) Nonoyama, S.; Yonezawa, N.; Saigo, K.; Hasegawa, M.; Hirano, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2387. (f) Lewis, F. R.; Reddy, G. D.; Elbert, J. E.; Tillberg, B. E.; Meltzer, J. A.; Kojima, M. *J. Org. Chem.* **1991**, *56*, 5311.

(5) (a) Chiba, T.; Okada, M.; Kato, T. *J. Heterocycl. Chem.* **1982**, *19*, 1521. (b) Naito, T.; Momose, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1982**, *30*, 1531. (c) Sato, M.; Kawakami, K.; Kaneko, C. *Chem. Pharm. Bull.* **1987**, *35*, 1319.

(6) Intramolecular [2+2] photocycloaddition reactions of 4-alkenyloxy-2-quinolones are known: (a) Kaneko, C.; Naito, T.; Somei, M. *J. Chem. Soc., Chem. Commun.* **1979**, 804. (b) Kaneko, C.; Suzuki, T.; Sato, M.; Naito, T. *Chem. Pharm. Bull.* **1987**, *35*, 112.

(7) **Representative Procedure for the Intermolecular [2+2] Photocycloaddition:**
A solution of quinolone **6** (767 mg, 2.03 mmol, 30.0 mM) and methacrylate (3.67 mL, 3.49 g, 40.5 mmol, 20 equiv, 0.6 M) in toluene (70 mL) was irradiated at 350 nm (RPR-3500 Å) in a merry-go-round apparatus at r.t. for 4 h. After removal of the solvent in vacuo, the crude product was purified by flash chromatography (silica 60: 5 × 20 cm, pentane–EtOAc = 50:50) to give 750 mg (80%) *rac*-**1a** as a white foam. ^{1}H NMR (360 MHz, DMSO-d_6, 80 °C): δ = 9.91 (s, 1 H, NH), 7.30–7.20 (m, 3 H, H_{ar}), 7.15–7.05 (m, 4 H, H_{ar}), 6.99 (virt. t, ^3J = 7.5 Hz, 1 H, H_{ar}), 6.89 (d, ^3J = 7.9 Hz, 1 H, H_{ar}), 4.27 (s, 2 H, CH_2Ph), 3.65 (s, 3 H, COOCH_3), 3.18 (virt. t., ^3J = 10.0 Hz, 1 H, C*H*COOMe), 3.01–2.90 (m, 2 H, CH*H*N, COCH), 2.72–2.58 (m, 2 H, CHCH*H*, C*H*HN), 2.38–2.19 (m, 1 H, CHC*H*H), 2.06–1.93 (m, 1 H, CC*H*H), 1.86–1.73 (m, 1 H, CCH*H*), 1.40 [s, 9 H, C(CH_3)$_3$]. ^{13}C NMR (90.6 MHz, DMSO-d_6, 80 °C): δ = 171.4 (*C*OOMe), 168.8 (CONH), 154.3 (*C*O*t*Bu), 138.1 (s, C_{ar}), 137.0 (s, C_{ar}), 127.9 (d, C_{ar}H), 127.6 (d, C_{ar}H), 127.0 (d, C_{ar}H), 126.6 (d, C_{ar}H), 125.7 (d, C_{ar}H), 124.5 (s, C_{ar}), 122.5 (d, C_{ar}H), 115.3 (d, C_{ar}H), 78.7 [*C*(CH$_3$)$_3$], 50.9 (COO*C*H$_3$), 49.7 (CH$_2$Ph), 48.8 (*C*HCOOMe), 44.8 (*C*CH$_2$), 41.7 (CH$_2$N), 39.2 (*C*HCH$_2$), 33.9 (C*C*H$_2$), 27.7 [C(*C*H$_3$)$_3$], 24.4 (C*C*H$_2$). Anal. calcd for $C_{27}H_{32}N_2O_5$ (464.55): C, 69.81; H, 6.94; N, 6.03. Found: C, 69.54; H, 6.79; N, 5.87.

(8) Review: Grosch, B.; Bach, T. In *CRC Handbook of Photochemistry and Photobiology*, 2nd ed.; Horspool, W. M.; Lenci, F., Eds.; CRC Press: Boca Raton, **2004**, 61–1.

(9) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K.; Herdtweck, E. *Synthesis* **2001**, 1395.

(10) For investigations on the binding of lactams to complexing agent **10**, see: (a) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982. (b) Bach, T.; Grosch, B.; Strassner, T.; Herdtweck, E. *J. Org. Chem.* **2003**, *68*, 1107. (c) Bergmann, H.; Grosch, B.; Sitterberg, S.; Bach, T. *J. Org. Chem.* **2004**, *69*, 970. (d) Grosch, B.; Orlebar, C. N.; Herdtweck, E.; Kaneda, M.; Wada, T.; Inoue, Y.; Bach, T. *Chem.–Eur. J.* **2004**, *10*, 2179.

(11) **Enantioselective Intramolecular [2+2] Photocycloaddition of Compound 8b:**
A solution of **8b** (20.0 mg, 5.84·10^{-2} mmol) and **10** (47.6 mg, 1.35·10^{-1} mmol) in toluene (8 mL) was degassed with argon. After cooling to –60 °C the solution was irradiated with a mercury high pressure arc (Original Hanau TQ 150) using a Duran filter in a merry-go-round apparatus at –60 °C for 8 h. After removal of the solvent in vacuo, the crude product was purified by flash chromatography (silica 60: 2 × 30 cm, CH_2Cl_2–MeOH = 98:2) to give 15.6 mg (78%) **2b** as a white solid (93% ee); 41.3 mg of the chiral complexing agent **10** were recovered. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.73 (s, 1 H, NH), 7.16 (dd, ^3J = 6.6 Hz, ^3J = 7.7 Hz, 1 H, H_{ar}), 7.08–6.95 (m, 2 H, H_{ar}), 6.86 (d, ^3J = 7.7 Hz, 1 H, H_{ar}), 3.72–3.63 (m, 2 H, NCH_2CH$_2$), 3.72–3.63 and 3.45 (d, ^2J = 14.0 Hz, 1 H, NCH*H*), 3.30 (dd, ^3J = 6.9 Hz, ^3J = 10.9 Hz, 1 H, C*H*), 3.22 and 3.08 (d, ^2J = 14.0 Hz, 1 H, NC*H*H), 2.62 and 2.54 (virt. t, ^3J = 12.0 and 11.7 Hz, 1 H, CHCH*H*), 2.44–2.24 (m, 1 H, NCH$_2$CH*H*), 2.05 (dd, ^3J = 6.9 Hz, ^3J = 12.5 Hz, 1 H, CHC*H*H), 1.90–1.77 (m, 1 H, NCH$_2$C*H*H), 1.50 and 1.49 [s, 9 H, C(CH$_3$)$_3$], 0.79 and 0.76 (s, 3 H, CH$_3$). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 172.6 and 172.4 (CONH), 155.9 and 155.3 (COOtBu), 136.6 (s, C_{ar}), 128.0 (d, C_{ar}H), 127.4 and 126.9 (d, C_{ar}H), 124.4 and 124.2 (s, C_{ar}), 123.3 (d, C_{ar}H), 116.1 (d, C_{ar}H), 79.7 [*C*(CH$_3$)$_3$], 50.5 and 48.6 (NCH$_2$), 43.5 and 43.0 (s, C_{al}), 42.0 (s, C_{al}), 39.8 and 39.4 (N*C*H$_2$CH$_2$), 36.1 and 35.5 (CH), 35.2 (CH*C*H$_2$), 32.4 and 31.9 (NCH$_2$*C*H$_2$), 28.5 [C(*C*H$_3$)$_3$], 23.5 (CH$_3$). [α]$_D^{20}$ –31.7 (*c* 0.4, $CHCl_3$). HRMS (EI): *m/z* calcd for $C_{20}H_{26}N_2O_3$: 342.1943. Found: 342.1935.