Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6927–6930

Novel reactions of 6,7-dimethoxy-3,4-dihydroisoquinoline and 3,4-dihydro-β-carboline with dipolarophiles

Miklós Nyerges,[a,*] András Dancsó,[b] István Bitter,[c] Gábor Blaskó[b] and László Tőke[c]

[a]*Organic Chemical Technology Research Group of the Hungarian Academy of Sciences, Budapest University of Technology and Economics, H-1521 Budapest, PO Box 91, Hungary*
[b]*EGIS Pharmaceuticals Ltd, H-1475 Budapest, PO Box 100, Hungary*
[c]*Department of Organic Chemical Technology, Budapest University of Technology and Economics, H-1521 Budapest, PO Box 91, Hungary*

Received 1 June 2005; revised 25 July 2005; accepted 1 August 2005

Abstract—New reactions of 6,7-dimethoxy-3,4-dihydroisoquinoline and 3,4-dihydro-β-carboline with various electron-deficient olefins are described. 'One-pot' generation and cycloaddition of the 1,3- and 1,4-dipoles formed from these heterocycles with a range of alkene dipolarophiles affords cycloadducts in good yields with high regio- and stereoselectivity.

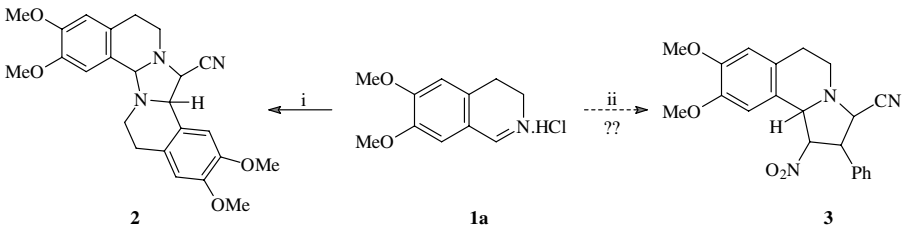
Dipolar cycloadditions, especially the most extensively studied bimolecular 1,3-version have found wide application in the synthesis of a great variety of heterocyclic systems. The importance of this reaction in organic synthesis is mainly due to its ability to generate five-membered heterocyclic rings containing several contiguous stereogenic centers in one synthetic operation.[1] Beside the large number of known routes,[2] the deprotonation of iminium salts is a very attractive method for the generation of azomethine ylides derived from nitrogen heterocycles.[3]

The 1,3-dipolar cycloadditions of azomethine ylides derived from dihydroisoquinolinium salts by deprotonation were previously studied in detail in our laboratory.[4] The dipoles produced by dehydrohalogenation were reacted with a wide range of dipolarophiles, for example, maleimides, maleates, β-nitro-styrenes, etc. We have also investigated the use of isoquinolinium salts in our new methodology applied for the simultaneous in situ generation of azomethine ylides and base-sensitive dipolarophiles.[5] Recently, we have described a simple one-pot process for the alkylation of dihydroisoquinoline **1a** followed by dehydrohalogenation of the quaternary salts and an in situ trapping of the azomethine ylides thus formed with several dipolarophiles.[6] During this study, chloracetonitrile or ethyl chloroacetate was used as alkylating agent. Our previous work, however, revealed that in the absence of any dipolarophile, this reaction also gave an unusual dimer **2** indicating that the dipole can react with the unreacted **1a** as dipolarophile.[4b] During our ongoing work to extend the utility of this one-pot method, the reaction was carried out with β-nitro-styrene, the formation of pyrrolo[2,1-*a*]isoquinoline cycloadduct **3** being expected (Scheme 1).

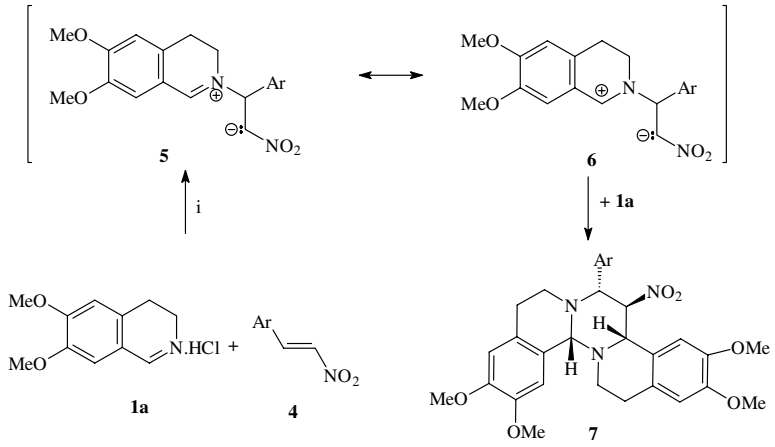
To our surprise, when a 1:1 molar mixture of 6,7-dimethoxy-3,4-dihydroisoquinoline **1a** and β-nitro-styrene (**4a** Ar = Ph) in EtOH was treated with an excess of either chloracetonitrile or ethyl chloroacetate at room temperature, the same product, hexahydro-isoquinolino[1′,2′:2,3]pyrimido[6,1-*a*]isoquinoline **7a** was formed in good yield (Scheme 2).[7,8] Similar results were obtained with a series of nitro-olefin analogues **4** (Table 1), the assignment of stereochemistry of the cycloadducts **7** being based on NOE data. To rationalise this transformation, we suggest initial addition of isoquinoline **1a** to β-nitro-styrenes **4** resulting in the formation of betaines **5**, the mesomeric form of which as 1,4-dipole **6** can react with an additional molecule of isoquinoline **1a** to give the pentacycles **7** as single diastereomers (Scheme 2).

Keywords: Azomethine ylides; Cycloadditions; Indoles; Isoquinolines.
* Corresponding author. Tel.: +36 1 4632213; fax: +36 1 4633648; e-mail: mnyerges@mail.bme.hu

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.08.006



Scheme 1. Reagents and conditions: (i) $ClCH_2CN$, Et_3N, EtOH, rt; (ii) $PhCH{=}CHNO_2$, $ClCH_2CN$, Et_3N, EtOH, rt.

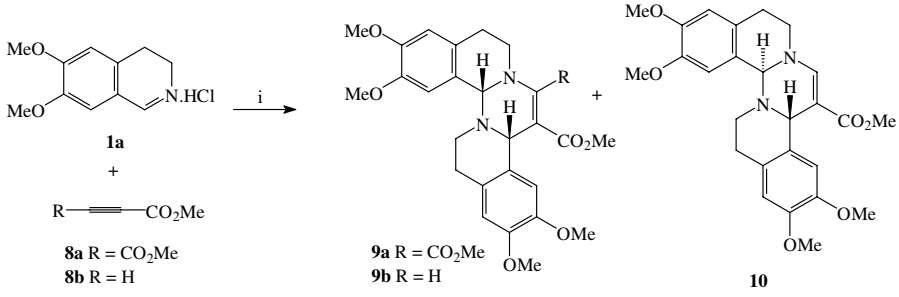


Scheme 2. Reagents and conditions: (i) Et_3N, EtOH, rt.

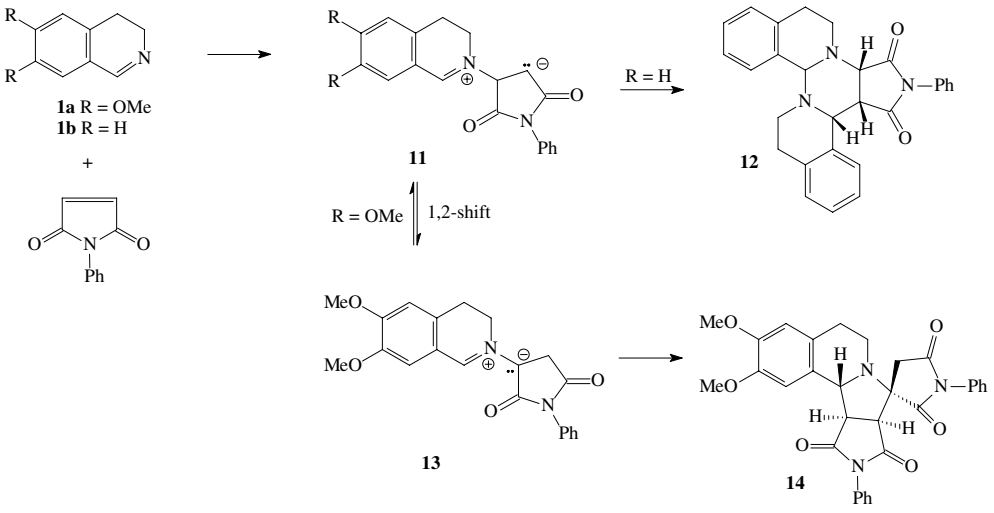
Table 1. Isoquinolino[1′,2′:2,3]pyrimido[6,1-*a*]isoquinolines prepared by the reaction of **1a** and **4**

Entry	Ar=	Product	Yield (%)
1	Phenyl-	**7a**	88
2	4-Methoxyphenyl-	**7b**	84
3	3-Methoxyphenyl-	**7c**	83
4	3,4-Dimethoxyphenyl-	**7d**	78
5	3,4-Methylendioxyphenyl-	**7e**	85
6	3-Nitrophenyl-	**7f**	92
7	4-Chlorophenyl-	**7g**	88
8	Trichloromethyl-	**7h**	65
9	3-Pyridyl-	**7i**	78
10	2-Furyl-	**7j**	69

The conceptual framework of 1,4-dipolar cycloadditions was laid down by Huisgen.[9] Reactions similar to ours have been described in his early studies[10] followed by other workers who observed this process as an unwanted side reaction during attempts to synthesise alkaloid derivatives.[11] Since then, such reactions have remained unexplored, except for some isolated reports[12] and the development of an intramolecular variant.[13] Therefore, aiming at assessing its scope and limits, we next chose to investigate the reaction of isoquinoline **1a** with dimethyl acetylenedicarboxylate **8a** (DMAD). The reactivity of nitrogen-containing heterocycles towards DMAD is well documented,[14] usually it involves the initial addition of the *N*-heterocycle to DMAD to form 1,4-dipolar intermediates, which undergo further reaction with DMAD leading to a variety of heterocyclic compounds.[15] Huisgen has already shown that the 1,4-dipole derived from 3,4-dihydroisoquinoline **1b** and DMAD can react with either DMAD or **1b** depending on the amount of DMAD used.[9a] The 1,4-dipole can also be trapped with external dipolarophiles,[10a] this



Scheme 3. Reagents and conditions: (i) Et_3N, EtOH, rt.



Scheme 4.

observation has been used in a number of novel three-component reactions.[16]

Interestingly, isoquinoline **1a** proved to be a more powerful dipolarophile than **1b** (and DMAD), as it gave exclusively the pentacyclic 2:1 adduct **9a** even with an excess of DMAD. A similar result was observed with methyl propiolate **8b**, however in this case a 1:1 mixture of stereoisomers **9b** and **10** was obtained (Scheme 3).

The reaction of **1b** and *N*-phenylmaleimide was investigated by Huisgen et al. and they obtained and characterised a 2:1 adduct **12** in moderate yield.[10c] In contrast, the 6,7-dimethoxy analogue **1a** behaved differently again, a novel spiro-heterocycle **14** precipitated from the ethanolic solution in good yield, even with excess of **1a**. The reaction starts with the addition of **1a** to *N*-phenylmaleimide affording the betaine **11** (vide infra), which converts by a formal 1,2-prototropy to azomethine ylide **13** capable of capturing another molecule of *N*-phenylmaleimide as dipolarophile (Scheme 4).[17] Only a few literature precedents are available for this type of 1,2-prototropic formation of azomethine ylides leading to spiroheterocycles.[18]

Finally, we studied the reactivity of 3,4-dihydro-β-carboline **15** with *N*-phenylmaleimide and nitro-olefins.[19] The reactions proceeded smoothly again at room temperature in EtOH giving products (**16** and **17**) in good yields, similar to those observed with **1a** (Scheme 5, Table 2).

Table 2. β-Carbolino[1′,2′:2,3]pyrimido[6,1-*a*]β-carbolines **16** prepared by the reaction of **15** with nitro-olefins

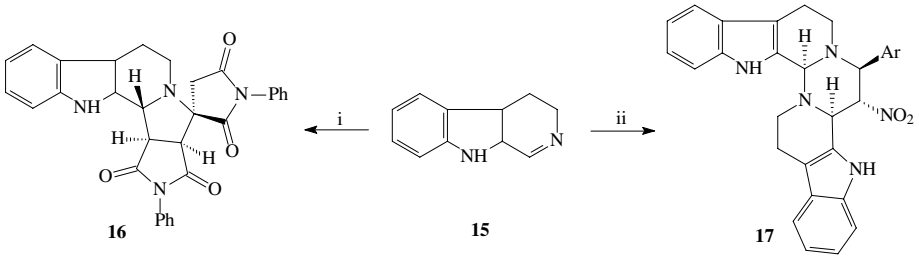
Entry	Ar	Yield (%)
1	Phenyl-	72
2	4-Methoxyphenyl-	66
3	3-Methoxyphenyl-	69
4	3-Nitrophenyl-	75
5	3-Pyridyl-	58

Acknowledgements

This work was financially supported by the National Fund for Science and Research, Hungary (OTKA Project No. T 046196). N.M. thanks the Hungarian Academy of Sciences for a Bolyai J. fellowship.

References and notes

1. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002.
2. Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231–349.
3. Sliva, W. *Curr. Org. Chem.* **2003**, *7*, 995–1048.



Scheme 5. Reagents and conditions: (i) *N*-phenylmaleimide (2 equiv) EtOH, rt (68%); (ii) ArCH=CHNO$_2$, EtOH, rt.

4. (a) Bende, Z.; Simon, K.; Tóth, G.; Tőke, L.; Weber, L. *Liebigs Ann. Chem.* **1982**, 924–929; (b) Bende, Z.; Bitter, I.; Tőke, L.; Weber, L.; Tóth, G.; Janke, F. *Liebigs Ann. Chem.* **1982**, 2146–2152; (c) Bende, Z.; Tőke, L.; Weber, L.; Tóth, G.; Janke, F.; Csonka, G. *Tetrahedron* **1983**, *40*, 369–375; (d) Tóth, G.; Tischner, T.; Bende, Z.; Szejtli, G.; Tőke, L. *Monatsh. Chem.* **1990**, *121*, 529–537; (e) Tischer, T.; Tőke, L.; Tóth, G. *Acta Chim. Hung.* **1990**, *127*, 171–172; (f) Janke, F.; Himmelreich, U.; Tóth, G.; Tischer, T.; Bende, Z.; Tőke, L. *J. Heterocycl. Chem.* **1991**, *28*, 867–873.
5. Fejes, I.; Nyerges, M.; Tőke, L.; Pak, C. S. *Tetrahedron* **2000**, *56*, 639–644.
6. Nyerges, M.; Somfai, B.; Tóth, J.; Dancsó, A.; Blaskó, G.; Tőke, L. *Synthesis* **2005**, 2039–2046.
7. For reports on the preparation of this heterocycle by other methods: (a) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M.; Yijun, C.; Anderson, A. P. *J. Am. Chem. Soc.* **1984**, *106*, 2680–2687; (b) Göndös, Gy.; Gera, L.; Tóth, G.; Kálmán, A.; Bridson, J. *Steroids* **1998**, *63*, 375–382; (c) Thesing, J.; Hofman, K. *Chem. Ber.* **1957**, *90*, 229–233; (d) Schaumann, E.; Mrotzek, H. *Chem. Ber.* **1978**, *111*, 661–672; (e) Schaumann, E.; Grabley, F.-F. *Liebigs Ann. Chem.* **1979**, 1702–1714; (f) Schaumann, E.; Grabley, F.-F. *Tetrahedron Lett.* **1980**, *21*, 4251–4254.
8. All new compounds afforded correct elemental analyses and spectroscopic data. Selected example: **7a**: ^{1}H NMR ($CDCl_3$, 500 MHz): 7.30 (5H, m, Ph), 7.10 (1H, s, H-13), 6.63 (1H, s, H-1), 6.57 (1H, s, H-10), 6.36 (1H, s, H-4), 5.04 (1H, t, *J* 10.0 Hz, H-5), 4.84 (1H, s, H-13b), 4.67 (1H, d, *J* 10.0 Hz, H-4b), 3.99 (1H, d, *J* 10.0 Hz, H-6), 3.85 (3H, s, OMe), 3.82 (3H, s, OMe), 3.81 (3H, s, OMe), 3.74 (3H, s, OMe), 3.05 (1H, m, H-15), 2.90 (1H, m, H-16), 2.87 (2H, m, H-9 and H-15), 2.84 (1H, m, H-8), 2.65 (1H, m, H-16), 2.43 (1H, m, H-9), 2.24 (1H, m, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz): 148.7 (q, C-2), 148.1 (q, C-11), 147.7 (q, C-12), 147.0 (q, C-3), 137.4 (q, Ph-1′C), 128.9 (5 × CH, Ph), 128.7 (q, C-9a), 126.65 (q, C-16a), 125.9 (q, C-13a), 125.0 (q, C-4a), 111.7 (CH, C-10), 110.7 (CH, C-1), 109.5 (CH, C-4), 108.7 (CH, C-13), 90.9 (CH, C-5), 81.4 (CH, C-13b), 72.1 (CH, C-6), 62.4 (CH, C-4b), 55.8 (OCH_3), 55.75 (OCH_3), 55.7 (OCH_3), 55.65 (OCH_3), 46.8 (CH_2, C-8), 38.3 (CH_2, C-15), 28.9 (CH_2, C-16), 28.5 (CH_2, C-9).
9. (a) Huisgen, R.; Herbig, K. *Liebigs Ann. Chem.* **1965**, *688*, 89–91; (b) Huisgen, R. In *Topics in Heterocyclic Chemistry*; Castle, R., Ed.; Wiley & Sons: New York, 1969, pp 223–252, Chapter 8.
10. (a) Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094–1106; (b) Huisgen, R.; Morikawa, M.; Breslow, D. S.; Grashey, R. *Chem. Ber.* **1967**, *100*, 1602–1615; (c) Huisgen, R.; Morikawa, M. *Chem. Ber.* **1967**, *100*, 1616–1620; (d) Huisgen, R.; Herbig, K.; Morikawa, M. *Chem. Ber.* **1967**, *100*, 1107–1115.
11. (a) Szántay, Cs.; Novák, L. *Chem. Ber.* **1967**, *100*, 2038–2048; (b) Whittaker, N. *J. Chem. Soc. (C)* **1969**, 85–89.
12. (a) Gothardt, H.; Riegels, M. *Chem. Ber.* **1988**, *121*, 1143–1146; (b) Dombrowski, A.; Nieger, M.; Niecke, E. *Chem. Commun.* **1996**, 1705–1706; (c) Valenciano, J.; Sanchez-Pavon, E.; Cuadro, A. M.; Vaquero, J. J.; Alvarez-Builla, J. *J. Org. Chem.* **2001**, *66*, 8528–8536.
13. For intramolecular 1,4-dipolar cycloadditions of cross-conjugated heteroaromatic betaines see: (a) Potts, K. T.; Dery, M. O. *J. Org. Chem.* **1990**, *55*, 2884–2894; (b) Potts, K. T.; Rochanapruk, T.; Padwa, A.; Coats, S. J.; Hadjiarapoglou, L. *J. Org. Chem.* **1995**, *60*, 3795–3805; (c) Padwa, A.; Harring, S. R.; Semones, M. A. *J. Org. Chem.* **1998**, *63*, 44–54.
14. Acheson, R. M.; Elmore, N. F. *Adv. Heterocyclic Chem.* **1978**, *23*, 263–285.
15. *For example:* Novikov, S. M.; Khlebnikov, A. F.; Sidorina, E. S.; Kostikov, R. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 231–237.
16. (a) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Bhadbhade, M. M.; Gonnade, R. C. *Org. Lett.* **2002**, 3575–3577; (b) Nair, V.; Sreekanth, A. R.; Biju, A. T.; Rath, N. P. *Tetrahedron Lett.* **2003**, *44*, 729–732; (c) Adib, M.; Mollahosseini, M.; Yavari, H.; Sayahi, M. H.; Bijanzadeh, H. R. *Synthesis* **2004**, 861–864.
17. Cycloadduct **14**: ^{1}H NMR ($CDCl_3$, 500 MHz): 7.52 (m, 4H, Ph-H), 7.45 (m, 2H, Ph-H), 7.42 (s, 1H, H-14), 7.23 (m, 4H, Ph-H), 6.75 (s, 1H, H-11), 4.53 (d, 1H, *J* 8.3 Hz, H-14b), 4.24 (d, 1H, *J* 9.8 Hz, H-3a), 3.74 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.69 (dd, 1H, *J* 8.3 and 9.8 Hz, H-14c), 3.65 (m, 1H, H-7), 3.36 (m, 2H, H-7 and H-9), 3.00 (m, 1H, H-10), 2.76 (m, 1H, H-10), 2.66 (m, 1H, H-9); ^{13}C NMR ($CDCl_3$, 125 MHz): 176.7 (q, C-1), 176.2 (q, C-3), 175.7 (q, C-4), 173.6 (q, C-6), 147.9 (q, C-12), 147.2 (q, C-13), 132.2 (q, Ph-1′C), 131.7 (q, Ph-1′C), 129.4 (2 × CH, Ph-3′ and 5′H), 129.3 (2 × CH, Ph-3′ and 5′H), 128.9 (CH, Ph-4′C), 128.4 (CH, Ph-4′C), 127.25 (2 × CH, Ph-2′ and 6′H), 127.2 (2 × CH, Ph-2′ and 6′H), 127.15 (q, C-14*a*), 126.1 (q, C-10*a*), 112.0 (CH, C-14), 109.7 (CH, C-11), 69.0 (q, C-3*b*), 55.7 (OCH_3), 55.5 (OCH_3), 53.8 (CH, C-3*a*), 49.5 (CH, C-14*c*), 42.1 (CH_2, C-9), 39.4 (CH_2, C-7), 28.9 (CH_2, C-10).
18. (a) Cookson, R. C.; Isaacs, N. S. *Tetrahedron* **1963**, *19*, 1237–1242; (b) Zirngibl, L.; Kunz, G.; Pretsch, E. *Tetrahedron Lett.* **1971**, 4189–4192; (c) Zirngibl, L.; Wagner-Jauregg, T.; Pretsch, E.; Stage, D. J.; Hales, N. J.; Paris, C. W. *Tetrahedron* **1971**, *27*, 2203–2209; (d) El-Emam, A. A.; Moustafa, M. A.; Eisa, H. M.; El-Kerdawy, M. M. *Heterocycles* **1986**, *24*, 1025–1029; (e) Grigg, R.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1995**, *51*, 13331–13346; (f) Mangalagiu, I. I.; Mangalagiu, G. C.; Petrovanu, M. *Heterocycles* **2001**, *55*, 365–370.
19. The reaction of this β-carboline and methyl vinyl ketone or its equivalent has been already described: (a) Szántay, Cs.; Tőke, L.; Honthy, K.; Kalaus, G. *J. Org. Chem.* **1967**, *32*, 423–427; (b) Winterfeldt, E.; Radunz, H. *Chem. Ber.* **1967**, *100*, 1680–1684.