Pergamon

Tetrahedron Letters 39 (1998) 4283–4286

TETRAHEDRON LETTERS

N-Phenyl-1-aza-2-cyano-1,3-butadienes : An Intramolecular Hetero Diels–Alder Strategy for the Construction of 1,4-Benzodiazepines

Catherine Goulaouic–Dubois, David R. Adams[1], Nicholas J. Sisti, Frank W. Fowler*[b], and David S. Grierson*[a]

a) Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif–sur–Yvette, France

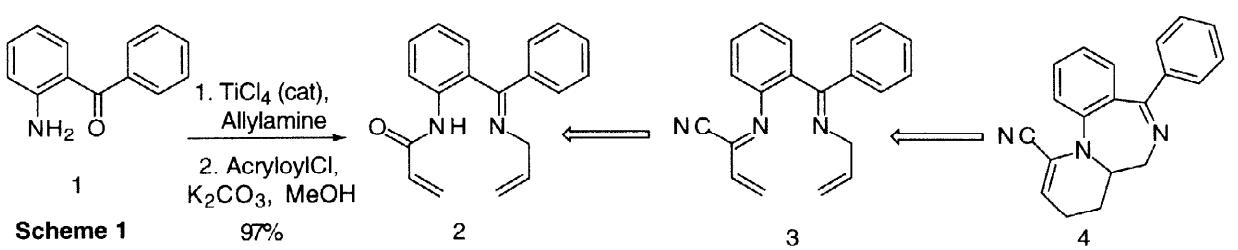
b) Department of Chemistry, SUNY, Stony Brook, New York 11794 , USA

Received 18 February 1998; accepted 8 April 1998

Abstract: A new approach to the construction of tricyclic 1,4-benzodiazepines has been developed, based upon the intramolecular Diels–Alder (IMDA) reaction of 2-cyano-1-azadienes. This study revealed the difficulties inherent to the direct transformation of imine-amide **2** to azadiene **3**, but demonstrated the efficiency of the intramolecular [4 + 2] cycloaddition of azadiene **13** as a means to access benzodiazepines **14a,b** (3 : 2 mixture; 74% combined yield).

A large number of medicinal agents and molecules displaying potent biological properties contain a benzodiazepine system in their structure. These include antidepressants,[2] GABA agonists/antagonists,[3] and antitumor agents.[4] Similarily, benzodiazepines are increasingly used as peptidomimetics in the construction of hydrolytically stable bioactive peptide like structures.[5]

In connection with projects that require novel polycyclic 1,4-benzodiazepines as intermediates, we have explored a new approach to this ring system based upon the intramolecular Diels-Alder (IMDA) reaction of 2-cyano substituted 1-azadienes (Scheme 1).[6-8] For example, to access 1,4-benzodiazepines possessing a tricyclic core such as **4**, the two key operations are: the elaboration of the N-aryl-2-cyano azadiene **3** from imine-amide **2**, and its intramolecular [4 + 2] cycloaddition. This latter step generates simultaneously the seven and six membered rings in the target molecule.

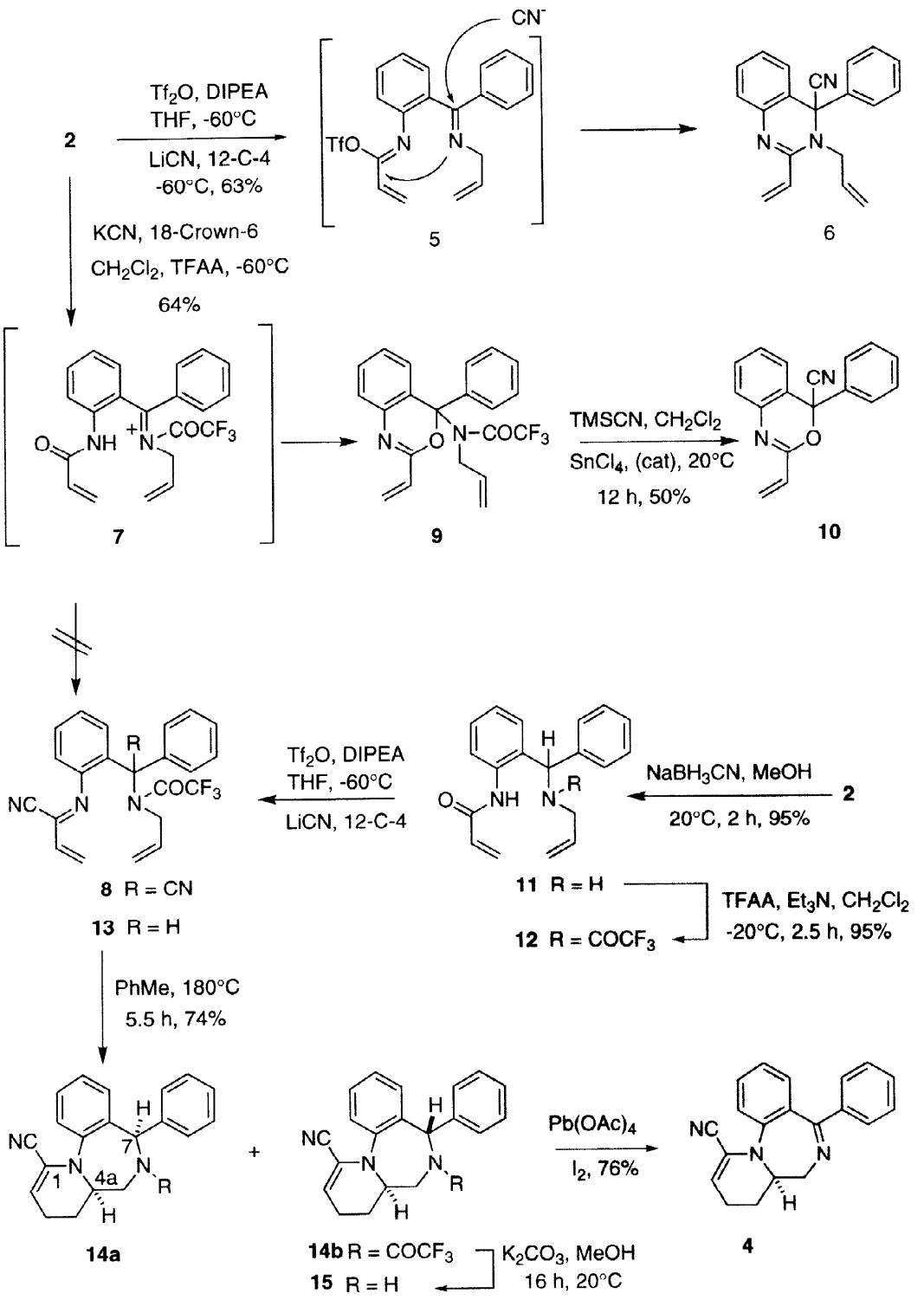


Scheme 1

Imine-amide **2** was readily prepared in 97% overall yield by successive reaction of 2-aminobenzophenone **1** with allyl amine-$TiCl_4$ (cat) (CH_2Cl_2, 20°C, 20 h) and acryloyl chloride (K_2CO_3, PhMe, 20°C).[9] However, treatment of this compound under our established conditions[7c] (Tf_2O and DIPEA at -60°C followed by LiCN)

* e-mail : grierson@icsn.cnrs-gif.fr

PII: S0040-4039(98)00756-4


Tf2O, DIPEA
THF, -60°C
LiCN, 12-C-4
-60°C, 63%
2
CN-
TfO
N
N
5
CN
N
N
6
KCN, 18-Crown-6
CH2Cl2, TFAA, -60°C
64%
O
NH
+
N
COCF3
7
N
O
N-COCF3
9
TMSCN, CH2Cl2
SnCl4, (cat), 20°C
12 h, 50%
CN
N
O
10
R
NC
N
N
COCF3
8 R = CN
13 R = H
Tf2O, DIPEA
THF, -60°C
LiCN, 12-C-4
H
O
NH
N
R
11 R = H
12 R = COCF3
NaBH3CN, MeOH
20°C, 2 h, 95%
2
TFAA, Et3N, CH2Cl2
-20°C, 2.5 h, 95%
PhMe, 180°C
5.5 h, 74%
H
NC
7
N
1
4a
N
R
H
14a
+
H
NC
N
N
R
H
14b R = COCF3
15 R = H
K2CO3, MeOH
16 h, 20°C
Pb(OAc)4
I2, 76%
NC
N
N
H
4

Scheme 2

led to the unique formation of dihydroquinazoline **6** rather than to the expected azadiene **3** (Scheme 2). This result demonstrated that the imine nitrogen in the *in situ* generated intermediate **5** acts as an internal nucleophile, competing effectively with cyanide ion for reaction with the imidoyl triflate function. To suppress formation of **6**, we subsequently explored conversion of **1** to **8** through reaction with trifluoroacetic anhydride/LiCN under Reissert reaction conditions.[10] In this way the imine function in **1** could be both masked and deactivated. However, an internal nucleophilic addition reaction was again observed, this time involving condensation of the acrylamide oxygen atom in the presumed intermediate **7** with the acyl iminium ion component to give oxazine **9**. Interestingly, attempts to transform compound **9** to the desired product through reaction with TMSCN/$SnCl_4$ (cat)[11] resulted in formation of the dihydro-1,3-oxazine product **10**. In other words, it was the *N*-allyltrifluoroacetamide component in the amino ether system in **9** which was activated with respect to departure, and not the oxygen atom.

It was thus apparent that for the Diels-Alder strategy to be effectively implemented it would be necessary to eliminate the imine function. The C=N double bond in **2** was thus selectively reduced using $NaBH_3CN$ in MeOH at 0 °C. The derived amine **11** was then protected as its trifluoroacetamide derivative **12** (TFAA, Et_3N, CH_2Cl_2; 95%). As expected, subsequent reaction of bis-amide **12** with Tf_2O and LiCN at -60°C led to formation of the desired azadiene **13**, isolated in 66% yield after flash column purification. [12]

With azadiene **13** in hand, its reactivity in the intramolecular Diels–Alder reaction mode was studied. In fact, this transformation proved to be efficient, leading on simple heating in toluene at 180 °C for 5.5 h to formation of a separable 3 : 2 mixture[12,13] of *cis*- and *trans*-benzodiazepines **14a** and **14b** in 74% total yield. The structures of the two cycloadducts were determined from their NMR data, and in particular from an nOe effect observed between H-4a and H-7 in the *cis* product **14a**. Analysis of the ^1H NMR spectra for these products was complicated, however, by peak doubling due to atropisomerism[14] resulting from restricted movement of the diarylmethane system, and/or differential population of amide rotomer conformations (peak ratios **14a** : 96/4; **14b** : 73/23).

Finally, the two step conversion of *trans*-**14b** to the target structure **4** was achieved by hydrolysis of the base labile trifluoroacetyl protecting group with K_2CO_3 in MeOH,[15] followed by oxidation of the liberated amine **15**[16] using $Pb(OAc)_4$ and iodine.[14] 1,4-Benzodiazepine **4** was thereby obtained in 76% yield.

Work is in progress to further extend this IMDA approach to the preparation of more highly functionalized 1,4-benzodiazepine structures, and to develop new methodology for the preparation of 2-cyano substituted 1-azadienes better adapted to our retrosynthetic strategy (Scheme 1).

Acknowledgements: Financial support for this work was provided by the Agence National de Recherche sur le SIDA (A.N.R.S.) Rhône-Poulenc Rorer is also gratefully acknowledged for its participation in the form of a Graduate Student Scholarship for one of us (C. G-D).

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12. **13**: ^{1}H ($CDCl_3$) δ 4.00-4.30 (m, CH_2), 4.55-4.86 (m, $=CH_2$), 5.15-5.46 (m, CH=), 6.05-6.24 (m, $=CH_2$), 6.56 (dd, J = 11, 17 Hz, CH=), 6.65 (s, CH); ^{13}C ($CDCl_3$) δ 49.13 (CH_2), 60.71 (ArCAr). **14a**: δ 1.40-2.30 (m, 4H, H-3, H-4), 3.21-3.72 (m, 2H, H-4a, H-5), 4.23 (d, J = 10 Hz, H-5), 5.42 (t, J = 4 Hz, H-2), 6.30 and 6.34 (s, H-7); δ 19.4, 26.0 (C-4, C-3), 47.84 (C-5), 59.2 (C-4a), 62.6 (C-7), 115.7, 119.2 (CN, C-1). **14b**: ($CDCl_3$) δ 1.32-1.82 (m, H-4), 2.14-2.37 (m, H-3), 3.25 and 3.98 (t, J = 13.5 Hz, 1H, H-5), 3.36 (t, J = 11 Hz, H-4a), 5.65-5.79 (s, H-2), 6.2-6.5 (s, H-7); δ 23.8 (C-3), 24.8 (C-4), 47.8 (C-5), 57.2 (C-4a), 63.5 (C-7), 114.8, 118.5 (CN, C-1).
13. The ratio of diastereomers **14** was determined for a crude product sample by HPLC (reverse phase C-18 radial compression 3.9 X 150 mm, eluant $MeOH/H_2O$ = 65/35, 1 mL/min, $t_{\mathbf{14b}}$ = 6.80 min, $t_{\mathbf{14a}}$ = 11.60 min .
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16. Peak doubling was again observed for amine **15**. In variable temperature ^{1}H NMR experiments signal coalescence was observed at 333 °K ($CDCl_3$), indicating that the energy barrier to conformational change (atropisomerism) is 15.25 kcal at 35°C.