$(CH_2)_nCH{=}CHR'$. Intersystem crossing to the singlet state is a major reaction of all triplet carbonylcarbenes that are not rapidly scavenged intramolecularly. Thus, with the exceptions outlined above, the lifetimes of carbonylcarbenes are controlled by the rate of spin inversion rather than by the reactivity of the triplet ground state.

Received: March 10, 1998 [Z11568IE]
German version: *Angew. Chem.* **1998**, *110*, 2352 – 2355

Keywords: carbenes · cyclizations · diazo compounds · rearrangements

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A New Heterocyclic Multicomponent Reaction For the Combinatorial Synthesis of Fused 3-Aminoimidazoles**

Hugues Bienaymé* and Kamel Bouzid

Combinatorial chemistry and high-throughput screening have changed, and are still changing, the face of modern drug discovery.[1] From the organic chemist's point of view, these new approaches emphasize the need for highly efficient and expeditious protocols. Multicomponent reactions—which combine two major principles of organic synthesis, convergence and atom economy—were prone to be recognized and used in library syntheses.[2] A prototypical example is the Ugi four-component reaction (Scheme 1),[3] though several other classical heterocyclic syntheses have also been used.[4] However, these transformations, which are of enormous potential value, remain scarce.[5] We therefore embarked on a program aimed at finding and exploiting *new* and *high-yielding* multicomponent reactions. Here we disclose our first results in this domain.

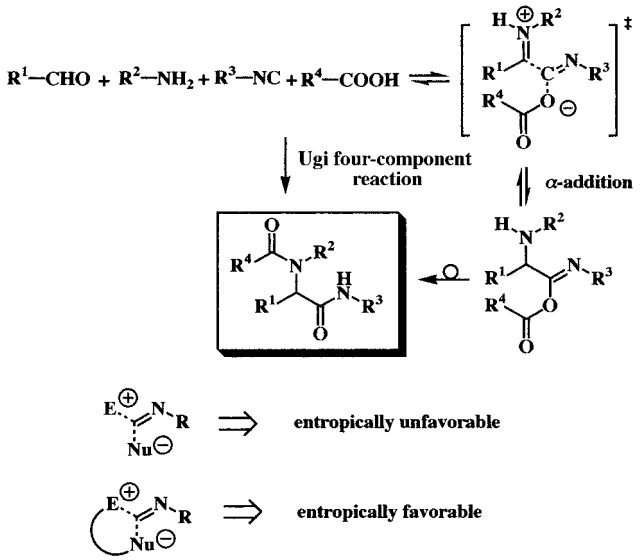
To be of industrial relevance, a multicomponent reaction should possess the following characteristics:

- It must be general enough to create libraries with 10 000 to 100 000 compounds (not a trivial situation!).
- It must be reliable (i.e., give high yields within its reactivity domain).
- It must be amenable to high-throughput automated synthesis (i.e., with a simple reaction protocol; ideally one would like to simply mix reactant solutions).

[*] Dr. H. Bienaymé, K. Bouzid
Rhône-Poulenc Technologies
BP 62, F-69192 St-Fons (France)
Fax: (+33) 4-72-93-67-21
E-mail: hugues.bienayme@rhone-poulenc.com

[**] We thank our colleagues from the analytical department (M. Lanson, L. Godde, J. L. Dumoulin, J. Guillaud-Saumur) for their skilled and dedicated contribution, the X-ray Structural Centre of the Russian Academy of Science for X-ray measurements, and Rhône-Poulenc for permission to publish these results.

  1433-7851/98/3716-2234 $ 17.50+.50/0

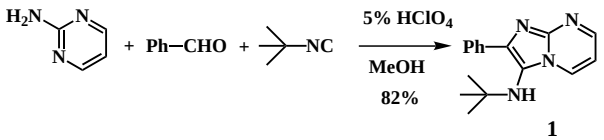


Scheme 1. The Ugi four-component reaction.

- It should give access to novel carbon frameworks, or known ones with original substitution patterns (an important feature when considering patenting libraries).[6]

When this program was started three years ago, no described reaction fulfilled all these requirements. We assumed that reliability problems associated with some multicomponent reactions with isonitriles arose from subtle kinetic and stereoelectronic factors in the key α-addition step (no less than three distinct functional groups must join simultaneously through covalent bonds). One way to overcome such an entropically unfavorable event is to create a covalent link between two reagents (Scheme 1).[7] Furthermore, original and patentable accesses to heterocyclic systems can be envisioned with this "bridging strategy".

Screening various substrate combinations in which an electrophile (a protonated iminium species, as in Ugi multicomponent reactions) and a nucleophile (a heteroatom) are linked, we found (partly by chance!) that heteroaromatic amidines, such as 2-aminopyridine or pyrimidine, reacted with isonitriles and aldehydes in the presence of a catalytic amount of protic acids by a very efficient new three-component reaction (Scheme 2). The structure of adduct **1** was established by ^{1}H and ^{13}C NMR and IR spectroscopy as well as



Scheme 2. Synthesis of 3-*tert*-butylamino-2-phenylimidazo[1,2-*a*]pyrimidine.

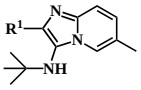
mass spectrometry, and confirmed by an X-ray diffraction study.[8] The high yield, simple reaction protocol, and originality of the 3-aminoimidazo[1,2-*a*]pyri(mi)dine ring system[9] prompted us to explore this unusual transformation more closely.

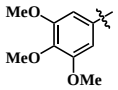
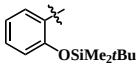
A preliminary study showed that methanol is the solvent of choice (substrate concentration $c = 0.3 - 0.5$ M), and that various protic acids can be used with almost equal success in this transformation (for instance, 0.05 – 0.10 equiv of perchloric acid). Aldehydes (1.2 – 3.0 equiv) and isonitriles (1.2 – 1.5 equiv) are best used in slight excess to the 2-aminoazine component. In most cases, reactions are fast at room temperature (2 – 12 h, 25 °C) and are not sensitive to oxygen or moisture. Thus, library syntheses could be carried out within 24 hours without heating in either vials or microtiter plate-formatted reactors (96 wells).

Tables 1 – 3 report (part of) the structural variations which are tolerated by this new multicomponent reaction. Aldehydes do not represent a major limitation to its scope (Table 1): Aromatic (electron-rich or electron-poor, entries 1 – 3, 9), aliphatic (even sterically encumbered, entries 4, 5), and heteroaromatic aldehydes (entries 6 – 8) all gave the corresponding products in excellent yields. The same is true for the different isonitriles (Table 3, entries 25 – 31).

As shown in Table 2, many heteroaromatic amidines can participate in this multicomponent reaction, though for most electron-poor amidines (entries 14, 16, 17, 21, 22) the reactions tend to be slow and side products accumulate. With these "borderline" cases an often encountered side product arises from the addition of methanol to the intermediate Schiff base (Scheme 3). For instance, with 2-amino-1,3,4-thiadiazole (entry 21) a nonnucleophilic solvent is used: trifluoroethanol. Very electron-poor amidines (2-amino-5-nitrothiazole or

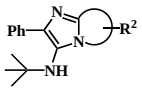
Table 1. Fused 3-aminoimidazoles: variation of the aldehyde (R^1).

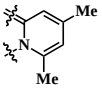
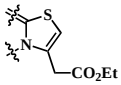
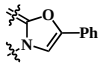
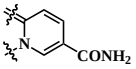
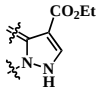


Entry	R^1	Yield[a] [%]	Entry	R^1	Yield[a] [%]
1		95	6		76[b]
2		98	7		98
3		84	8		96
4		95	9		92
5		94			

[a] Yields refer to isolated, purified compounds. The identity of the new compounds was determined by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis and/or high-resolution mass spectrometry. [b] Yield of crystalline compound isolated by filtration (no recovery from mother liquor); hence, the total yield may be higher.

Table 2. Fused 3-aminoimidazoles: variation of the amidine (R^2).



Entry	R^2	Yield[a] [%]	Entry	R^2	Yield[a] [%]
10		95	18		95
11		98	19		60[b]
12		90	20		86[b]
13		80[b]	21		76[c]
14		69	22		50
15		87	23		94[b]
16		75	24		33[b]
17		82			

[a], [b] See Table 1. [c] Trifluoroethanol was used as solvent.

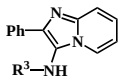
adenine, data not shown) and aliphatic amidines (benzamidine or 2-amino-2-thiazoline, data not shown) remain unchanged under these conditions.

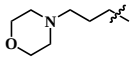
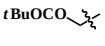
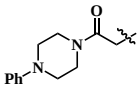
A probable mechanism which accounts for most of the observed results involves a (nonconcerted) [4+1] cycloaddition[10] between the protonated Schiff base (which holds both the electrophile and nucleophile) and the isonitrile (which behaves as a vinylidene carbenoid). A subsequent prototropic shift gives the final aromatic fused 3-aminoimidazole (Scheme 3).

Though protonated Schiff bases of 2-aminopyridines are known to undergo [4+2] cycloadditions with electron-rich olefins,[11] this is the first example of a [4+1] cycloaddition involving these species.

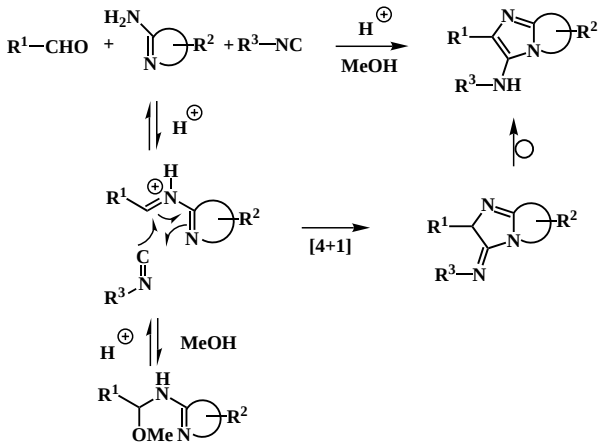
Thus, by virtue of the bridging strategy, we have discovered a highly efficient and practical approach to fused 3-aminoimidazoles of high structural diversity. With this chemistry almost 30000 different compounds have been prepared in our laboratories, either by parallel or small-mixture syntheses.[12]

Table 3. Fused 3-aminoimidazoles: variation of the isonitrile (R^3).



Entry	R^3	Yield[a] [%]	Entry	R^3	Yield[a] [%]
25		90	29		93
26		95	30		53[b]
27		86	31		40
28		90			

[a], [b] See Table 1.



Scheme 3. Mechanistic rationale for the synthesis of fused 3-aminoimidazoles.

Experimental Section

Typical procedure for the preparation of fused 3-aminoimidazoles: 3-*tert*-Butylamino-2-(2-pyridyl)-6-methylimidazo[1,2-*a*]pyridine: 2-Amino-5-picoline (0.415 g, 3.84 mmol) is dissolved in methanol (8 mL). Pyridine-2-carbaldehyde (0.62 g, 5.79 mmol) and *tert*-butylisonitrile (0.50 mL, 4.42 mmol) are added at room temperature (22 °C). A 1 M solution of perchloric acid in methanol (0.38 mL) is added, and the formation of the strongly UV-active adduct is followed by TLC (CH_2Cl_2/MeOH, 10/1; R_f = 0.45). After 18 h at room temperature the crude reaction mixture is diluted with dichloromethane (50 mL) and extracted successively with water (50 mL), a saturated solution of glutamic acid (pH 10, 20 mL), and brine (50 mL). After filtration over a short $MgSO_4$ pad, the crude reaction mixture (1.10 g) is evaporated and crystallized by adding diethyl ether (3 mL) and then pentane (6 mL, slowly). Pale yellow crystals are collected (0.821 g, 76 %). M_r = 280.37; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, HMDS): δ = 1.03 (s, 9H), 2.17 (s, 3H), 5.30 (br s, 1H), 6.81 (dd, 1H, J = 9, 1.5 Hz), 6.99 (ddd, 1H, J = 7.5, 5, 1 Hz), 7.31 (d, 1H, J = 9 Hz), 7.61 (ddd, 1H, J = 8, 7.5, 1 Hz), 7.94 (br s, 1H), 8.05 (br d, 1H, J = 8 Hz), 8.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 18.2, 29.9, 56.9, 116.7, 120.5,

  1433-7851/98/3716-2236 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 16

121.0, 121.3, 121.6, 126.9, 128.4, 134.7, 136.2, 140.7, 148.1, 155.1; IR (KBr): $\tilde{\nu}$ = 3336, 2965, 1589, 1571, 1441, 1390, 1358, 739 cm^{-1}; MS: *m*/*z*: 280, 223, 196.

Received: March 11, 1998 [Z11576IE]
German version: *Angew. Chem.* **1998**, *110*, 2349 – 2352

Keywords: combinatorial chemistry · cycloadditions · heterocycles · multicomponent reactions

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[8] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101255. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[9] A similar multicomponent access to 3-aminoimidazo[1,2a]pyridines was recently disclosed: a) C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.*, in press; for other routes, see b) J.-L. Moutou, M. Schmitt, V. Collot, J.-J. Bourguignon, *Tetrahedron Lett.* **1996**, *37*, 1787 – 1790; c) J. C. Teulade, R. Escale, H. Viols, J. P. Chapat, G. Grassy, A. Carpy, J. M. Léger, *J. Chem. Soc. Perkin Trans. I* **1983**, 2663 – 2667; d) G. Saint-Ruf, B. Loukalou, C. N′Zouzi, *J. Heterocycl. Chem.* **1981**, *18*, 1565 – 1570; e) N. W. Bristow, P. T. Charlton, D. A. Peak, W. F. Short, *J. Chem. Soc.* **1954**, 616 – 629.

[10] [4 + 1] Cycloaddition of isonitriles with various heterodienes is known, though none of the reported examples are of synthetic value in the context of high-throughput synthesis: a) S. Marcaccini, *Org. Prep. Proced. Int.* **1993**, *25*, 141 – 208, and references therein; b) C. Buron, L. El Kaïm, A. Uslu, *Tetrahedron Lett.* **1997**, *38*, 8027 – 8030; c) J. A. Deyrup, M. M. Vestling, W. V. Hagan, H. Y. Yun, *Tetrahedron* **1969**, *25*, 1467 – 1478.

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[12] Library syntheses and purification will be reported separately.

Occurrence of Cationic Intermediates and Deficient Control during the Enzymatic Cyclization of Squalene to Hopanoids**

Catherine Pale-Grosdemange,* Corinna Feil, Michel Rohmer,* and Karl Poralla

Triterpenes belong to a group of natural products for which the theme of enzymic polyene cyclization is rich in variations. Such cyclizations—including the formation of all cyclic isoprenoids, regardless of the series to which they belong—produce the most diverse array of natural products.[1, 2] Concerning only triterpenes, about 100 different skeletons are found in nature.[3] Owing to genetic techniques and new purification procedures, highly purified squalene-hop-22(29)-ene cyclase (SHC) is now available without any contamination by cellular lipids.[4] This cyclase, like lanosterol and cycloartenol cyclase, catalyzes the most sophisticated one-step reaction known in biochemistry.[5] For the formation of the hopane skeleton, 13 covalent bonds are broken or formed, 9 chiral centers are established, and 5 rings are produced. The reaction is thought to be sensitive to side reactions because of the postulated occurrence of reactive carbocationic intermediates.[6] Furthermore, exclusion of water from the active site is also a problem for SHC as hopan-22-ol (**3**, diplopterol) is always produced along with hop-22(29)-ene (**2**, diploptene).[6]

Several minor hydrocarbons are produced along with diploptene (**2**) upon the SHC-catalyzed cyclization of squalene (**1**). The presence of such triterpenes helped explain the intermediacy of tetra- and pentacyclic carbocations during the formation of the hopane skeleton. Upon analyzing the products of the enzymatic cyclization of squalene (**1**) by GLC, peaks for minor products (each representing 0.9 – 2 % of the area of the peak for diploptene) were observed between the peaks corresponding to squalene and diploptene. The same product distribution also appeared when testing a highly purified SHC without a His tag, which was otherwise necessary for purification on a nickel affinity column. Preliminary GC-MS results showed that all these compounds had a relative molecular mass of 410 and were isomers of squalene and diploptene.

These compounds were separated by thin-layer chromatography on silica gel impregnated with silver nitrate (argenta-

[*] Prof. Dr. M. Rohmer, Dr. C. Pale-Grosdemange
Institut Le Bel, Université Louis Pasteur
4 rue Blaise Pascal, F-67070 Strasbourg (France)
Fax: (+33) 3-88-41-61-01
E-mail: mirohmer@chimie.u-strasbg.fr
Dr. C. Feil, Prof. Dr. K. Poralla
Biologisches Institut der Universität
Mikrobiologie/Biotechnologie
Auf der Morgenstelle 28, D-72076 Tübingen
E-mail: poralla@uni-tuebingen.de

[**] We wish to thank Thomas Härtner for production and isolation of the crude fraction of triterpenes, Jean-Daniel Sauer for all NMR measurements, Estelle Nastio and Jacques Blanzat for recording mass spectra, and Dr. Pierre Albrecht (ULP, Strasbourg) for the gift of a neohopene sample. The collaboration was supported by the Deutsche Forschungsgemeinschaft (SFB 323) and a grant to M.R. from the Alexander von Humboldt Foundation.

  1433-7851/98/3716-2237 $ 17.50+.50/0