MCR IX[1]: A NEW AND EASY WAY FOR THE PREPARATION OF PIPERAZINE-2-KETO-3-CARBOXAMIDES

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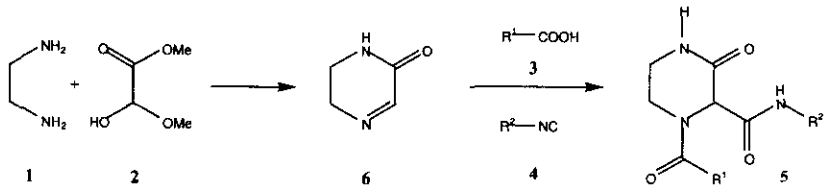
Abstract - Piperazine-2-keto-3-carboxamides (**5**) are formed by an one-pot U-4CR (Ugi four component reaction) between ethylenediamine (**1**), glyoxylic acid-hemiacetal (**2**), a carboxylic acid (**3**) and an isocyanide (**4**).

The early classical 3CR´s[2] (three component reaction) of α-aminoalkylations and their secondary reactions as well as the chemistry of the isocyanides[3] were investigated in the same century. This area ended around 1960, when the isocyanides became well available,[3-5] and a new type of MCR´s (multi component reaction) of the isocyanides was developed. In 1959 the U-4CR was introduced[6] and this was also the beginning of a new area of isocyanides and a great variety of three and more other educts, that equilibrate together with intermediate products, to form the desired final products irreversibly.[7,8] Thus, instead of the usual amines and carbonyl compounds, the three or four educts of an Asinger reaction can participate[7,9] as an imine, or instead of a carboxylic acid an alcohol and CO_2 can be used.[2] In some cases the intermediate products of U-4CR´s can be combined with nucleophiles, forming thus products of five components.[8,10]

Recently some suitable bi-functional components can form piperazines and substituted piperazine derivates. Some of them are important pharmacophores.[11,12]

K. Rossen *et al.*[13] have published the preparation of some piperazine-2-carboxamides from *N*-alkylethylendiamin, chloracetaldehyde, a carboxylic acid and an isocyanide. Such products are only obtained by purification with flash chromatography and their final yields are between 34 - 67%.

Our new syntheses of 2-ketopiperazine derivatives (**5**) are U-4CR´s between ethylenediamine (**1**), glyoxylic acid-hemiacetal (**2**), carboxylic acids (**3**) and isocyanides (**4**).



Scheme 1: 4CR to the 2-ketopiperazine derivatives

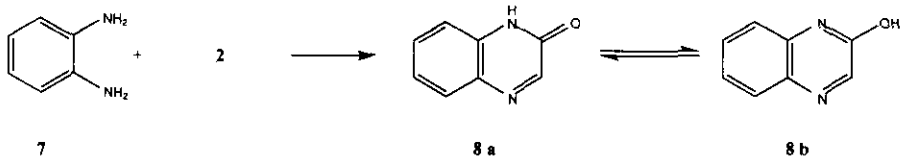
It is in fact very easy to perform such reactions: in tetrahydrofuran as solvent, an equimolar mixture of the four components is refluxed for 24 hours and the product is obtained by removing the solvent. The advantage of this reaction corresponds to a direct one-pot procedure. Their yields are almost quantitative and no tedious purification is needed.

The first step of this reaction is the condensation between the ethylenediamine (**1**) and the aldehyde derivate(**2**). The complete formation of the cyclic imine (**6**) is the reason why this reaction proceeds with a variety of isocyanides (R^2 = metyl, *tert*-butyl, cyclohexyl) and carboxylic acids (R^1 = H, methyl, trifluormethyl, phenyl).

Table 1: 2-Ketopiperazine derivatives

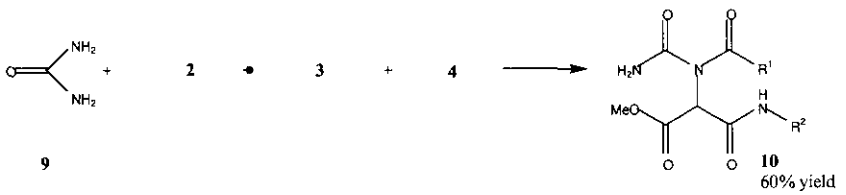
carboxylic acid (**3**) R^1	isocyanide (**4**) R^2	piperazine-2-keto-3-carboxamide (**5**) yield (%)
methyl	*tert*-butyl	**5a,** quantitative
trifluormethyl	methyl	**5b**, quantitative
phenyl	*tert*-butyl	**5c**, quantitative
H	cyclohexyl	**5d**, quantitative
H	*tert*-butyl	**5e**[14], quantitative

1,2-Phenylenediamine (**7**) forms in nearly quantitative yield the aromatic product (**8**).



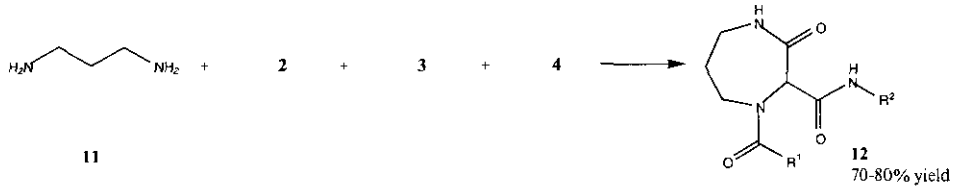
Scheme 2: Condensation of phenylenediamine and glyoxylic acid-hemiacetal

In an attempt to form a cyclic product from urea (**9**) like a diamino component, product (**10**) is formed.



Scheme 3: 4CR with urea

In analogy, the 7-membered 2-keto-1,4-diazepin-system (**12**) is obtained from 1,3-propylenediamine (**11**) by a similar MCR.



Scheme 4: 2-Keto-1,4-diazepin-system by using from 1,3-propylendiamine

Summary: Piperazine-2-keto-3-carboxamides we prepared from the cyclization of ethylenediamine (**1**), glyoxylicacid-hemiacetal (**2**), a carboxylic acid (**3**) and an isocyanide (**4**) by an efficient and flexible one-pot MCR has been developed.

REFERENCES

1. I. Ugi and T. Schmid, *J. prakt. Chem.*, in press.
2. H. Hellmann and G. Opitz, *α-Aminoalkylierung*, Verlag Chemie, Weinheim, **1960**.
3. I. Ugi, *Isonitrile Chemistry*, Academic Press, New York, **1971**.
4. I. Ugi and R. Meyr, *Angew. Chem.*, **1958**, *70*, 702.
5. R. Obrecht, R. Hermann, and I. Ugi, *Synthesis*, **1985**, 400.
6. I. Ugi, R. Meyr, U. Fetzer, and C. Steinbrückner, *Angew. Chem.*, **1959**, *71*, 386.
7. I. Ugi, A. Dömling, and W. Hörl, *Endeavour*, **1995**, *18/3*, 115.
8. I. Ugi, *Proc. Estonia Acad. Sci. Chem*, **1995**, *44/4*, 237.

9. A. Dömling and I. Ugi, *Angew. Chem.*, **1993**, *105*, 634, *Angew. Chem., Int. Ed. Engl.*, **1993**, *31*, 563.
10. A. Demharter, W. Hörl, E. Hertweck, and I. Ugi, *Angew. Chem.*, **1996**, *108*, 185, *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 173.
11. *Idem*, *J. Med. Chem.*, **1994**, *37*, 3443.
12. E. Mishani, C. S. Dence, T. J. McCarthy, and M. J. Welch, *Tetrahedron Lett.*, **1996**, *37*, 319.
13. K. Rossen, J. Sager, and L. M. DiMichele, *Tetrahedron Lett.*, **1997**, *38*, 3183.
14. All piperazines are prepared by the following procedure: A mixture of 10 mmol of each components in 80 mL of tetrahydrofuran is refluxed for 24 h. The reaction mixture is evaporated and the product resulted in quantitative yield.
The ^{1}H, ^{13}C and MS data are in agreement with the proposed structures. **5e** is a 2:1 rotameric mixture. **5e** (DMSO- d_6, 360 MHz, Bruker). Major rotamer- ^{1}H NMR (δ in ppm): 8.15 (s, 1H, NH); 8.01 (s, 1H, COH); 7.59 (s, 1H, NH); 4.79 (s, 1H, CH); 3.68 (d, J = 12.9 Hz, 1H, CH_2); 3.42 (m, 1H, CH_2); 3.13 (m, 2H, CH_2); 1.1 (s, 9H, $C(CH_3)_3$). Minor rotamer- ^{1}H NMR (δ in ppm): 8.25 (s, 1H, NH); 7.88 (s, 1H, COH); 7.68 (s, 1H, NH); 4.74 (s, 1H, CH); 3.97 (d, J = 12.8 Hz, 1H, CH_2); 3.42 (m, 1H, CH_2); 3.13 (m, 2H, CH_2); 1.13 (s, 9H, $C(CH_3)_3$). Major rotamer- ^{13}C NMR (δ in ppm): 164.81 (CO); 164.02 (CO); 161.19 (CHO); 56.92 (CH); 50.28 ($C(CH_3)_3$); 40.79 (CH_2); 39.78 (CH_2); 27.98 ($C(CH_3)_3$). Minor rotamer- ^{13}C NMR (δ in ppm): 164.87 (CO); 164.18 (CO); 161.81 (CHO); 60.26 (CH); 50.38 ($C(CH_3)_3$); 40.49 (CH_2); 34.41 (CH_2); 27.92 ($C(CH_3)_3$).

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