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Effect of high pressure on sterically congested Passerini reactions

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Abstract—The effect of high pressure is examined in 3-CC (Passerini) reactions. This effect is small when moderately hindered reactants are involved. However, particularly in the case of bulky isocyanides, the sensitivity of the reaction to pressure increases with increasing steric congestion in line with earlier studies described in the reference list. Such a result highlights the synthetic utility of high pressure activation for the preparation of hindered Passerini products.

In former times, the practice of evaluating pharmaceutical properties rested on random screening of targeted organic compounds synthesized one *per* one according to conventional ways. To remedy the time consuming repetitive efforts, combinatorial technologies have emerged and are now manifested as a powerful tactic for the simultaneous preparation of a myriad of new products.[1] These strategies are mostly based on one-pot multicomponent addition or condensation reactions in which three or four reactants combine in a single reaction event. The whole set of products synthesized in this way is called library.

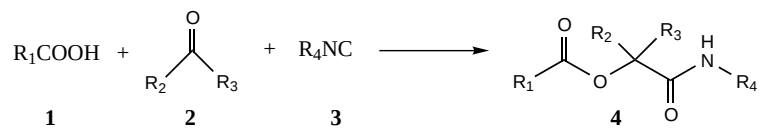
Multicomponent reactions have been discovered for a long time (Mannich, Strecker) and have been since enriched in this century with the Passerini reaction[2] and, more recently, Ugi reaction.[3] The present paper is concerned with Passerini reactions, also called 3-CC reactions. They consist of the reaction of isocyanides **3** with carboxylic acids **1** and carbonyl compounds **2** to yield compounds **4** in a single step (Eq. (1)).

Such reactions usually work well and are little affected by the size of R_1, R_2, R_3, R_4, apparently meaning that Passerini reactions are relatively insensitive to steric effects.[4] However, the debate remains open since the severity of steric bulk in the components was not thoroughly examined in 3-CC reactions and hardly in Ugi reactions.[5] As an interesting result, sterically hindered Ugi reactions may lead to the Passerini reaction as a side reaction.[5] It was also reported that some congested ketones and carboxylic acids do not react with isocyanides according to the Passerini process.[6]

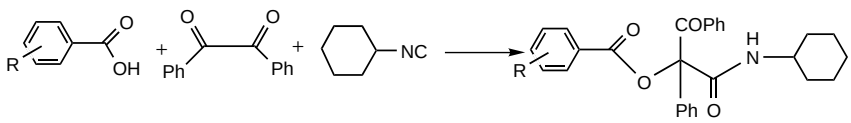
Since a relationship could be established between the magnitude of steric effects and pressure,[7] we were interested in examining the influence of pressure on Passerini reactions involving components featured by variable steric bulk manifested in R_1, R_2, R_3, R_4.

The reactions investigated proceeded cleanly and yielded selectively compounds **4**, which were characterized unambiguously by NMR spectroscopy.[8] Analytical data are given for two compounds which could be synthesized only at higher pressure.[8] The results are listed in Tables 1–3.

In a first step, we examined the 3-CC reaction involving benzoic acids, benzile and cyclohexyl isocyanide (Eq. (2)). This reaction was studied by Passerini who showed that only one carbonyl bond of the diketone reacted[2] (Table 1).



(1)



(2)

Keywords: Passerini reactions; isocyanides; steric effects; pressure.

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Table 1. Effect of the structure of benzoic acid[a] (Eq. (2))

Entry	R	Yields (%)		β
		0.1 MPa	300 MPa	
1	H	20	33	1.7
2	CH_3 (*ortho*)	18	28	1.6
3	CH_3 (*meta*)	13	24	1.8
4	CH_3 (*para*)	10	20	2.0

[a] Acid (0.6 mmol), cyclohexyl isocyanide (0.44 mmol), benzile (0.40 mmol), solvent (diethyl ether), 25°C, reaction time (16.5 h). β is the ratio of yields at 0.1 and 300 MPa, respectively.

As inferred by the results exposed in Table 1, substitution of aromatic hydrogen by a methyl group induces only a slight moderation of the yield. The pressure effect expressed by β (ratio of yields reached at ambient and 300 MPa pressure, respectively, under identical experimental conditions) is modest and barely depends on the size and position of R.

Using aliphatic carboxylic acids, we varied the bulk of R_1 in Eq. (1) (Table 2). The size of R_1 influences directly the yield at normal pressure. This is particularly highlighted in the case of butyric acids (entries 6–8). Interestingly, the pressure effect now depends on steric constraints. β increases with increasing bulkiness of R_1. When the ketone is made bulkier and *t*-butyl isocyanide is reacted, the reaction becomes very sensitive to pressure as the yield increases from 2.2 to 51.8% in the 300 MPa pressure range (entry 9).

Lastly, we investigated the effect of the size of R_3 (in ketone) and R_4 (isocyanide), keeping the same acid (*p*-toluic acid) throughout the series (Table 3) (Eq. (3)).

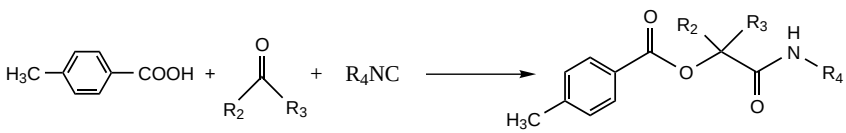
Table 3. Effect of the structure of the keto compound and isocyanide[a] (Eq. (3), $R_2=CH_3$)

Entry	R_3	R_4	Yields (%)		β
			0.1 MPa	300 MPa	
10	C_6H_5	Cyclohexyl	12	27	2.2
11	CH_3	nC_4H_9	23	46	2.0
12	CH_3	Cyclohexyl	17	40	2.4
13	CH_3	tC_4H_9	12	47	3.9
14	C_2H_5	nC_4H_9	19	48	2.5
15	C_2H_5	Cyclohexyl	15	36	2.4
16	C_2H_5	tC_4H_9	7	52	7.4
17	iC_3H_7	nC_4H_9	18	36	2.0
18	iC_3H_7	Cyclohexyl	20	39	2.0
19	iC_3H_7	tC_4H_9	5	39	7.8
20	iC_4H_9	nC_4H_9	7	30	4.3
21	iC_4H_9	tC_4H_9	1	12	12
22	tC_4H_9	nC_4H_9	7	29	4.1
23	tC_4H_9	tC_4H_9	0	13 (73)[b]	High

[a] Acid (0.4 mmol), isocyanide (0.5 mmol), ketone (reactant and solvent), 25°C, reaction time (16.5 h).
[b] Yield at 600 MPa.

increasing complexity of R_3 (compare the gradual increase of β in entries 13, 16, 19, 21, 23).

Entry 23 highlights a Passerini reaction which does not proceed at all at ambient pressure under conditions of Table 3 due to steric inhibition. This reaction afforded a yield of 13% at 300 MPa and 73% at 600 MPa. The pressure effect on steric hindrance was clearly exemplified in Fig. 1 with the aid of two reactions described in entries 15 and 16. At normal pressure, as expected, the yield of the Passerini product obtained from *n*-butyl isocyanide was much higher than the corresponding



(3)

At ambient pressure, yields depend both on the size of R_3 and R_4 (compare for example, entries 11, 14, 17, 20, 22). However, with moderately bulky ketones and isocyanides, the pressure effect was roughly identical, β varied between 2 and 2.5 (entries 10, 11, 12, 14, 15, 17, 18). In runs involving *t*-butyl isocyanide, the reactions were clearly more pressure sensitive, particularly with adduct synthesized from *t*-butyl isocyanide. However, at pressures higher than 300 MPa the reaction involving the more crowded isocyanide afforded a higher yield. At 450 MPa the latter reaction afforded a nearly quantitative yield. Such reaction profiles resemble those described in an earlier paper reporting the pressure dependence of yields in the synthesis of hindered functionalized ethers.[9]

Table 2. Effect of the structure of the carboxylic acid[a] (Eq. (1), $R_2=CH_3$)

Entry	R_1	R_3	R_4	Yields (%)		β
				0.1 MPa	300 MPa	
5	CH_3	CH_3	Cyclohexyl	41	89	2.2
6	nC_4H_9	CH_3	Cyclohexyl	16	51	3.2
7	iC_4H_9	CH_3	Cyclohexyl	9	38	4.2
8	tC_4H_9	CH_3	Cyclohexyl	6	28	4.7
9	tC_4H_9	CH_3	tC_4H_9	2	52	26

[a] Acid (0.4 mmol), isocyanide (0.5 mmol), ketone (reactant and solvent), 25°C, reaction time (16.5 h).

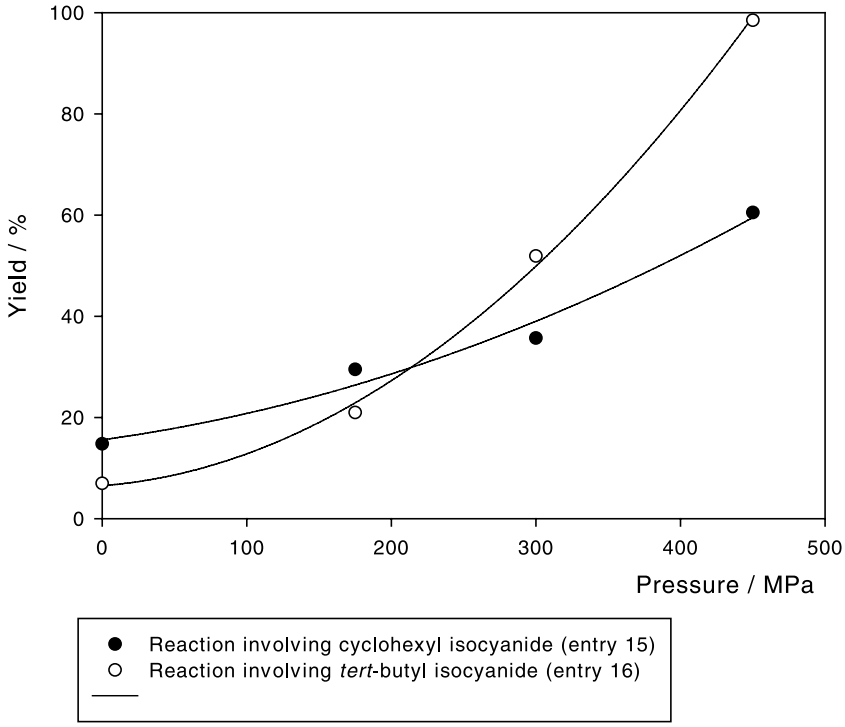
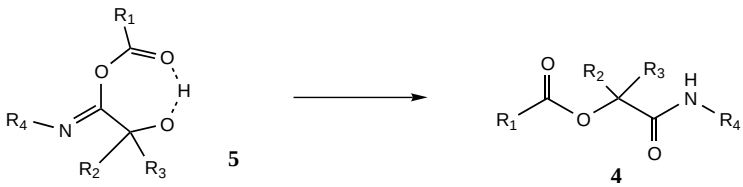


Figure 1. Effect of pressure on the chemical outcome in the Passerini reactions described in entries 15 and 16.



Scheme 1.

A plausible three-stage mechanism of the 3-CC reaction has been devised.[3] The formation of a cyclic transition state containing all three substrates should be intuitively promoted by pressure (Scheme 1). However, the effect is difficult to predict as this formation results from two equilibria, which are not necessarily strongly influenced by pressure, although it seems reasonable to assume a preferential shifting to the right. Also, it depends on the rate determining step. The cyclic transition state would lead to the intermediate **5**, whose rearrangement to product **4** should be modestly pressure sensitive (Scheme 1). The major pressure effect detected in the present hindered Passerini reactions is, therefore, a consequence of steric constraints. The result is of primary importance and stays in full harmony with those previously reported in our laboratory.[7,9,10]

Conclusion

In conclusion, for unhindered and weakly hindered Passerini reactions, the pressure effect is low and more or less identical regardless of the size of alkyl or aromatic groups beared by the three components. However, particularly when *t*-butyl isocyanide is involved, sterically demanding reactions are much more pressure sensitive. The sensitivity is directly related to the overall steric constraints of the reaction. Since bioactivity can be heavily dependent on steric parameters (considered as the interaction of the bioactive substance with the biological receptor site),[11] the high pressure method exposed in this paper offers an attractive tactic to synthesize sterically congested Passerini products **4** (Eq. (1)).

References

1. (a) Weber, L.; Wallbaum, S.; Broger, C.; Gubernator, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2280–2282; (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131; (c) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144–154.
2. Passerini, M. *Gazz. Chim. Ital.* **1924**, *54*, 529.
3. Review: Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.

4. Yamada, T.; Motoyama, N.; Taniguchi, T.; Kazuta, Y.; Miyazawa, T.; Kuwata, S.; Matsumoto, K.; Sugima, M. *Chem. Lett*. **1987**, 723–726.
5. Ugi, I.; Marquarding, D.; Urban, R. *Chemistry and Biochemistry of Amino Acids*, *Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1982; Vol. 6, Chapter 6.
6. Müller, E.; Zech, B. *Liebigs Ann. Chem*. **1966**, *696*, 72–80.
7. Jenner, G. *J. Chem. Soc., Faraday Trans. 1* **1985**, *81*, 2437–2460.
8. Experimental procedure: The carboxylic acid, bibenzyl (internal standard about 0.12 mmol) and ketone were placed in a flexible 2.5 mL PTFE tube. The isocyanide was then added dropwise. The volume was adjusted either with the solvent (ether) or the corresponding ketone depending on run. The tube was shaken and rapidly introduced into the high pressure vessel. After release of pressure the volatile compounds were removed in vacuo. The residue was directly analyzed by ^{1}H NMR and the yield determined from relative intensities of characteristic protons versus methylene protons of the internal standard. We report NMR data for unprecedented Passerini adducts. Spectroscopic data for **4** (entry 9): ^{1}H NMR ($CDCl_3$): 5.21 (s, 1H, NH), 1.56 (s, 3H, CH_3), 1.25 (s, 9H, CH_3 from isocyanide), 1.15 (s, 9H, CH_3 from acid), 0.97 (s, 9H, CH_3 from ketone); ^{13}C NMR ($CDCl_3$): 169.7, 164.4, 130.8–129.7, 30.3, 29.0, 26.4, 21.6, 18.1.
For **4** (entry 23): ^{1}H NMR (acetone-d_6): 7.98 (d, 2H, aromatics), 7.24 (d, 2H, aromatics), 4.95 (s, 1H, NH), 2.24 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.21 (s, 9H, CH_3 from isocyanide), 1.02 (s, 9H, CH_3 from ketone); ^{13}C NMR (acetone-d_6): 176.4, 169.6, 30.3, 28.9, 27.5, 26.1, 17.8.
9. Jenner, G. *Tetrahedron Lett*. **2001**, *42*, 4807–4810.
10. Jenner, G. *High Press. Res*. **1992**, *11*, 21–32.
11. Fujita, T.; Iwamura, H. *Top. Curr. Chem*. **1983**, *114*, 119–157.