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# Synthesis of hindered functionalized ethers via high-pressure addition of alcohols to acrylic compounds

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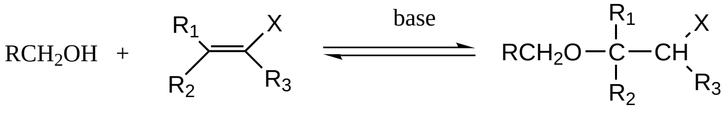
**Abstract**—The phosphine-catalyzed 1,4-addition of alcohols to activated alkenes is studied from a synthetic point of view. α- or β-Substituted acrylic compounds react sluggishly or not at all. In this case, high-pressure activation can remove steric inhibition leading to good yields of the corresponding ethers. Reactions involving crotonic compounds (hindered β reaction center) show higher pressure dependence than the corresponding additions of alcohols to methacrylic analogs (free β reaction center). This is in agreement with the concept that sterically demanding reactions show enhanced sensitivity to pressure. The result, obviously, is of high synthetic value as pressure may be capable of removing steric inhibition. © 2001 Elsevier Science Ltd. All rights reserved.

As part of an ongoing program directed toward evaluating the effects of steric hindrance on high-pressure reactions,[1] we became interested in specific nucleophilic reactions. The addition of alcohols to activated alkenes is a well-known reaction.[2] Hetero-Michael reactions involving alcohols occur under mild conditions either inter-[3] or intramolecularly.[4] Much emphasis is usually placed on the 1,4-addition of acrylonitrile with alcohols. The process is called cyanoethylation.[5] The reaction is an easy and convenient method for the preparation of a large number of quite interesting multifunctional compounds. Unfortunately, the reaction does not tolerate sterically encumbered substrates. Unlike acrylonitrile, unsaturated nitriles substituted by alkyl groups on the α or β carbon usually react with extreme difficulty requiring harsh conditions (strong base, elevated temperatures, prolonged reaction times) to give acceptable yields.[2] In fact, it fails utterly in most cases. The paucity of data in this field led us to develop an interest in these reactions.

The considered reaction is a Michael-like addition only occurring in the presence of a base. It is a multistep process. It involves the formation of the alkoxy carbanion in the initial stage followed by nucleophilic attack on the electrophilic β position of the acrylic compound. This step is rate determining. A rapid proton transfer yields the final product.

The pressure effect has been considered in related schemes.[6,7] Since the rate-determining step is bimolecular, $S_N2$ reactions should undergo rate acceleration on application of pressure, simply via reduction of the reaction volume. However, it was shown that the effect of pressure in the process was actually complex. The transition state is highly dipolar so that solvation effects must be taken into account. Even the counterion seemingly plays a specific role. The situation is further complexed by the possibility of reverse reactions, particularly in the rate-determining step.[8]

The synthetic issue of the pressure reaction depends therefore, on the magnitude of the overall activation volume. It was shown to amount ca. $-20$ cm$^3$ mol$^{-1}$ in the base-catalyzed Michael addition of nitromethane to methyl vinyl ketone.[8] Based on this value, the pressure induced speeding up of the rate of these molecular transformations should contribute to afford fair to



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good yields of functionalized ethers. As an illustrative example, sterically hindered nitroalcohols could be synthesized mainly at high pressures according to Henry processes which exhibit similar activation volumes.[8]

We, therefore, examined the pressure effect on the nucleophilic addition of unbranched primary alcohols to acrylic compounds (nitriles, amides, ketones, methyl esters). All reactions were carried out neat in the given primary alcohol in the presence of tri-*n*-butylphosphine (the selection of the base will be justified in a forthcoming paper). The results are listed in Table 1 reporting the yields obtained when ROH is ethanol. Following comments are in order:

- At ambient pressure steric-free reactions centers are extremely reactive (entries 1, 6 and 8). However, acrylamide does not add under conditions due to the poorly activated amido group (entry 4). Methacrylonitrile (entry 2) and crotononitrile (entry 3) also react though at a lower rate than acrylonitrile does, despite the substitution at α and β positions.
- Pressure is unquestionably exerting a positive directive effect on yields. This is demonstrated in entries 2 and 3. A 300 MPa pressure brings the reactions to completion or almost. Even acrylamide adds though poorly (entry 4). The reaction involving mesityl oxide is precluded at ambient pressure as a result of the prohibitive bulk of the two *gem*-β-methyl groups. However, increasing the pressure to 800 MPa affords a 35% yield of the corresponding adduct (entry 7).[10] Under the same pressure methacrylamide also reacts leading to a modest 10% yield (entry 5).

Considering these results, an interesting observation can be made. Reactions involving acrylic compounds with reduced accessibility at the β reaction center (entries 3, 7, and 10) are clearly more pressure dependent than their unhindered analogs (entry 4) or even those substituted at the α-position (entries 2, 5, and 9).

Taking into account this observation, we were moved to consider in a second stage the influence of the alkyl part of the alcohol keeping a given acrylic compound throughout. This was done by examining the addition of linear primary $C_1$–$C_5$ alcohols to cinnamonitrile ($R_1=H$, $R_2=Ph$, $R_3=H$, $X=CN$). This acrylic nitrile showed strong reluctance to enter addition due to the congested β reaction center (phenyl group) (Table 2).

According to Table 2, it is clear that the steric behavior of the alcohol conditions the yield of cyanoether. The size of the alkyl rest R is overriding. Only methanol reacts under ambient pressure. Pressure in excess of 300 MPa induces an obvious accelerating effect. At 800 MPa excellent yields are obtained with lower primary alcohols and fair reactivity is observed with higher alcohols. The results indicate that the cyanoalkylation with hindered unsaturated nitriles is a highly pressure dependent reaction.

In a last step, we tried to support the correlation between the accelerating effect of pressure and steric congestion by investigating the respective addition of 1-propanol and 1-butanol to methacrylonitrile (α substituted reaction center) and crotononitrile (having a β substituted methyl group). Figs. 1 and 2 diagrammatically represent the yields. It can be observed that the crotononitrile reactions (A and C) are more affected by pressure than the respective methacrylonitrile reactions (B and D). These results verify our earlier statement that sterically demanding reactions are subjected to enhanced sensitivity to pressure.[11] The results presented here open the way to synthetic possibilities which otherwise are not available by classical routes.

**Table 2.** Addition of linear primary alcohols to cinnamonitrile (conditions as in Table 1; time: 24 h)

| ROH | Yields (%) at various pressures | | |
|---|---|---|---|
| | 0.1 MPa | 300 MPa | 800 MPa |
| $CH_3OH$ | 13 | 73 | No run |
| $C_2H_5OH$ | 0 | 31 | No run |
| $C_3H_7OH$ | 0 | 10 | 96 |
| $C_4H_9OH$ | 0 | 4 | 80 |
| $C_5H_{11}OH$ | 0 | 0 | 48 |

**Table 1.** Addition of ethanol to acrylic compounds[a]

| Entry | X | $R^1$ | $R^2$ | $R^3$ | Time (h) | Yields (%) at various pressures | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 0.1 (MPa) | 300 (MPa) | 800 (MPa) |
| 1 | CN | H | H | H | 2 | 99 | nr | nr |
| 2 | CN | H | H | $CH_3$ | 3 | 33 | 78 | nr |
| 3 | CN | H | $CH_3$ | H | 3 | 32 | 99 | nr |
| 4 | $CONH_2$ | H | H | H | 24 | 0 | 5 | 9 |
| 5 | $CONH_2$ | H | H | $CH_3$ | 24 | 0 | 0 | 10 |
| 6 | $COCH_3$ | H | H | H | [b] | 100 | nr | nr |
| 7 | $COCH_3$ | $CH_3$ | $CH_3$ | H | 24 | 0 | 0 | 35 |
| 8 | $COOCH_3$ | H | H | H | 3 | 53[c] | nr | nr |
| 9 | $COOCH_3$ | H | H | $CH_3$ | 3 | 5 | 19 | nr |
| 10 | $COOCH_3$ | H | $CH_3$ | H | 3 | 3 | 30 | nr |

[a] Acrylic compound (1.8 mmol), tributylphosphine (0.3 mmol), ethanol (0.8 mL), 50°C; nr, no run.

[b] Instantaneous reaction.

[c] The dimer of methyl acrylate was also formed resulting from a Morita–Baylis–Hillman reaction.[9]

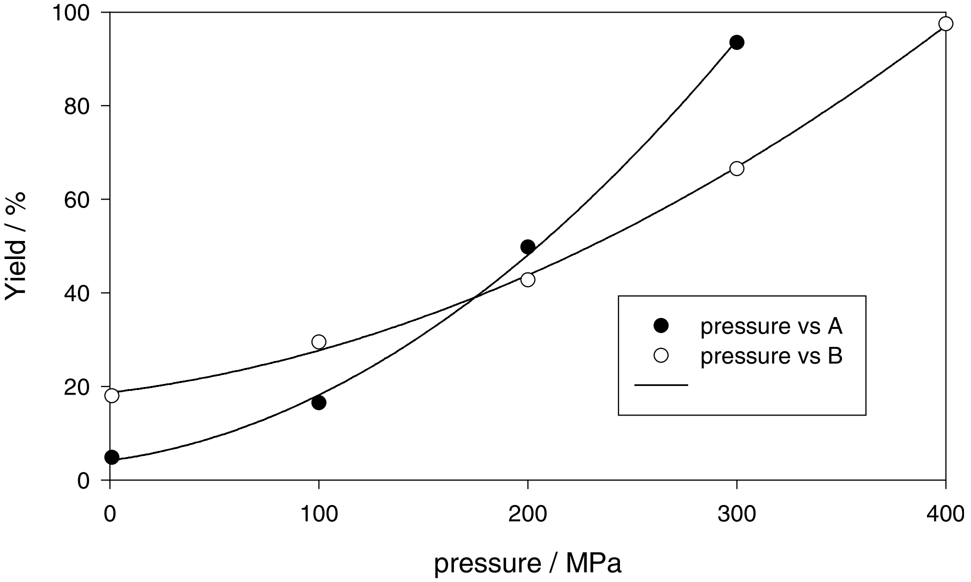

**Figure 1.** Effect of pressure in the addition of ethanol to crotononitrile (A) and methacrylonitrile (B) (conditions as in Table 1; reaction time: 4 h).

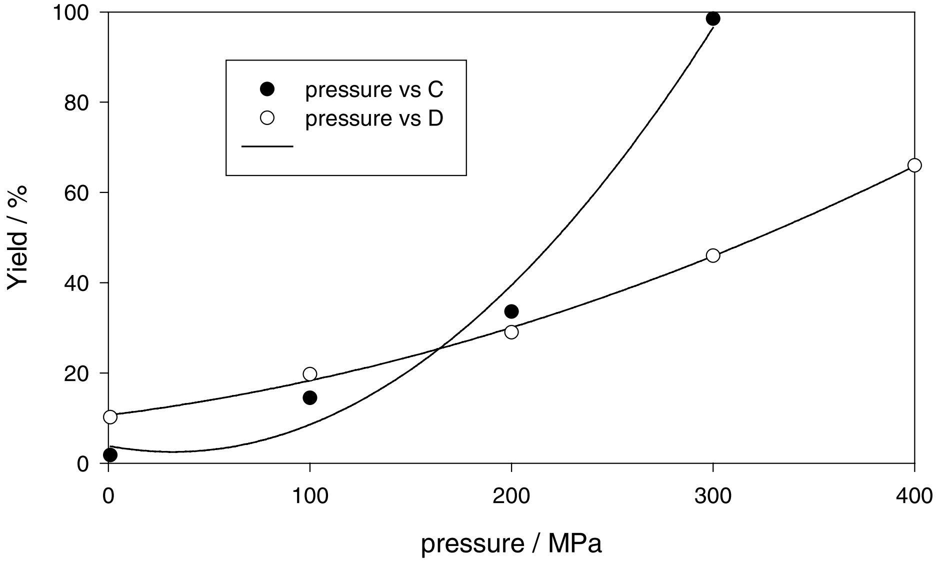

**Figure 2.** Effect of pressure in the addition of butanol to crotononitrile (C) and methacrylonitrile (D) (conditions as in Table 1; reaction time: 4 h).

## Conclusions

In the tri-*n*-butylphosphine-catalyzed addition of primary alcohols to hindered unsaturated acrylic compounds, the salient features are:

- the beneficial though variable effect of pressure in the synthesis of sterically hindered functionalized ethers
- the remarkable capacity of the pressure parameter to remove steric inhibition

In conclusion, in harmony with our earlier studies related to the pressure effect in sterically congested reactions,[1,11,12] pressure is a powerful way to overcome the lethargy of reaction centers frozen by steric requirements. This interesting facet of piezochemistry will be developed in a forthcoming full paper.

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