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Molybdenum hexacarbonyl mediated synthesis of indolin-2-one & azaindolin-2-one under catalyst free conditions

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ABSTRACT

Syntheses of indolin-2-ones and azaindolin-2-ones have been realized. The strategy involves the formation of tosylhydrazone from tosylhydrazine and 2-amino aryl or pyridyl aldehydes/ketones which then undergo intramolecular aminocarbonylation to afford indolin-2-ones and azaindolin-2-ones. The generality of the method was demonstrated by synthesizing C3 substituted and unsubstituted indolin-2-one and azaindolin-2-one derivatives.

The 2-oxindole is present as a core nucleus in a number of biologically active natural products, drug molecules, and agrochemicals.[1] The significance of 2-oxindole in drug discovery has been well established as a number of drugs having this nucleus are already in the market for treatment of various diseases.[2] For example, Sunitinib (Fig. 1) has been approved and marketed for the treatment of renal cell carcinoma and Imatinib resistant GIST; whereas Toceranib phosphate (Fig. 1) is used for the treatment of canine cutaneous mast cell tumors.[2]

The significance of oxindoles in chemical and pharmaceutical industry prompted us to develop a new strategy for its synthesis. The most commonly used method employ cyclization strategy,[3] derivatization of heterocycle,[4] metal-catalyzed cyclocarbonylations,[5] intramolecular Heck couplings of 2-haloacryloylanilides[6] and photochemical methods.[7] Although most of these methods are widely used for the generation of oxindoles, limitations remain because of functional group compatibility, expensive metal catalyst, and prolonged reaction time. Recently ultrasound promoted clay catalyzed synthesis of oxindoles has been reported.[8] However; this method has practical limitations at a higher scale and remains restricted only to unsubstituted C3 oxindoles. We proposed to carry out the synthesis of indolin-2-one and 2-azaindolin-2-one from tosylhydrazone of 2-aminobenzaldehyde and 2-aminopyridine-3-carbaldehyde, respectively, via intramolecular aminocarbonylation in the presence of $Mo(CO)_6$. The tosylhydrazone is a versatile synthetic intermediate and gained special attention after the discovery of Barluenga boronic acid coupling (BBA) reaction under metal free conditions.[9] Recently, a palladium free aminocarbonylation of tosylhydrazone with $Mo(CO)_6$ has been reported by Reddy and co-workers (Scheme 1).[10]

To the best of our knowledge there is no report for the synthesis of indolin-2-one or azaindolin-2-one using catalyst free intramolecular aminocarbonylation strategy.

The synthesis commenced with the formation of tosylhydrazone (**2**) of 2-aminobenzaldehyde (**1**).[11] The resulting tosylhydrazone was dissolved in dioxane and heated at 110 °C in the presence of DBU as a base. We were delighted to observe the formation of indolin-2-one (**3**) in 80% isolated yield[12] (Scheme 2).

This result was particularly encouraging, as we obtained yields comparable to the intermolecular aminocarbonylation[10] that employed conventional heating. Next, we screened a variety of solvents and bases and results have been summarized in Table 1.

The solvents did not have much effect on the yields but the nature of the base had a significant effect. Among DBU, DIPEA, KOtBu, and Cs_2CO_3 only DBU furnished the desired product in satisfactory yields (entries 1–4). With other bases the conversion was either slow or afforded unwanted products. The optimized reaction conditions were next applied to tosylhydrazone (**5**) which was

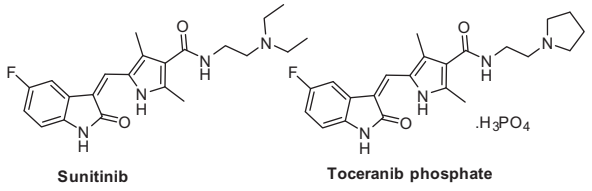

Figure 1. 2-Oxindole based drug.

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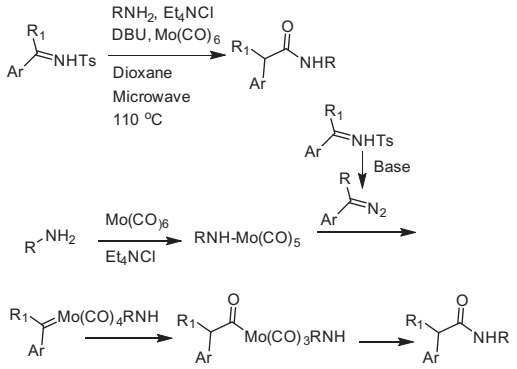
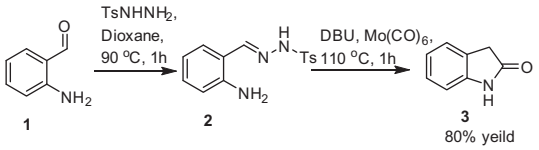


Scheme 1. Reddy and co-workers work and proposed mechanism.

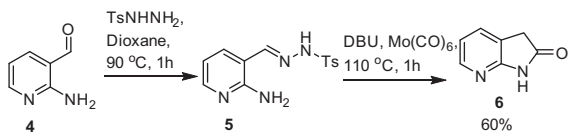


Scheme 2. Synthesis of indolin-2-one.

Table 1
Effect of solvent and base

Entry	Solvent	Base	Time (h)	Yield[a] (%) of **3**
1	Dioxane	DBU	1.0	80
2	THF	DBU	1.0	75
3	Toluene	DBU	1.0	72
4	DME	DBU	1.0	76
5	Dioxane	DIPEA	1.0	Major starting material
6	Dioxane	Cs_2CO_3	1.0	No reaction[b]
7	Dioxane	KOtBu	1.0	No reaction[b]

[a] Isolated yield.
[b] Starting material consumed but desired product was not formed.



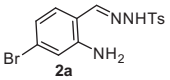
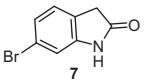
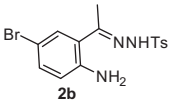
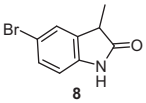
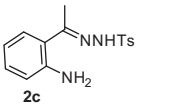
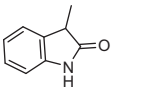
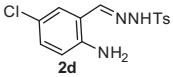
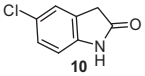
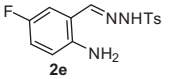
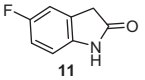
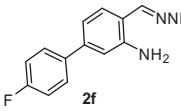
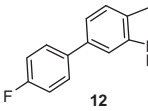
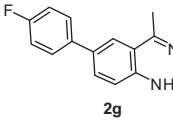
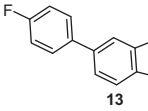
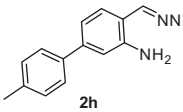
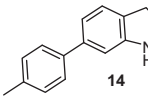
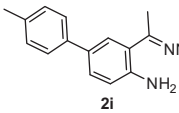
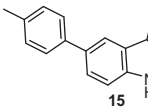
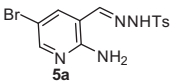
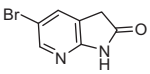
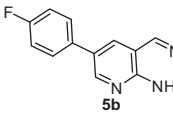
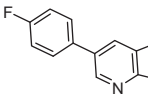
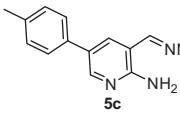
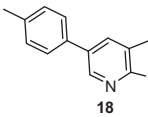
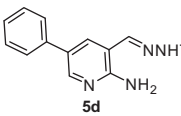
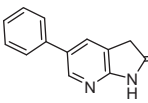
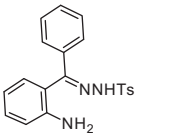
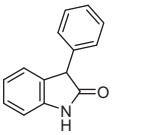
Scheme 3. Synthesis of azaindolin-2-one.

obtained by treating 2-amino pyridine carbaldehyde (**4**) with tosylhydrazine (Scheme 3). The reaction afforded azaindolin-2-one **6**, but the yield (60%) was lower as compared to indolin-2-one **3**.

Finally, the optimized conditions were applied to synthesize a variety of substituted indolin-2-one and azaindolin-2-one derivatives.[13] The results have been summarized in Table 2.

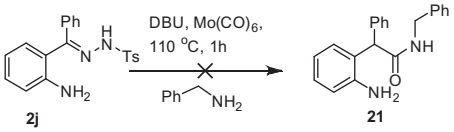
As depicted in Table 2, a variety of indolin-2-ones and azaindolin-2-ones were successfully synthesized. Attempt to synthesize the C3 phenyl substituted indolin-2-one (**20**) from corresponding **2j** was not successful. This may be attributed to steric factors arising from the presence of the phenyl group, thereby interfering with the intramolecular aminocarbonylation. In a separate experiment, benzyl amine was added to the reaction mixture (Scheme 4) which failed to afford the intermolecular aminocarbonylation product **21**. This clearly indicates the involvement of other factors along with steric factor.

Table 2
Synthesis of indolin-2-ones and azaidolin-2-ones

Entry	Tosylhydrazone	Product	Yield[a] (%)
1	 **2a**	 **7**	55
2	 **2b**	 **8**	53
3	 **2c**	 **9**	65
4	 **2d**	 **10**	50
5	 **2e**	 **11**	55
6	 **2f**	 **12**	60
7	 **2g**	 **13**	56
8	 **2h**	 **14**	52
9	 **2i**	 **15**	56
10	 **5a**	 **16**	53
11	 **5b**	 **17**	50
12	 **5c**	 **18**	57
13	 **5d**	 **19**	54
14	 **2j**	 **20**	0

[a] Isolated yield.

In conclusion, we have developed a very efficient and catalyst free method for the synthesis of substituted indolin-2-one and



Scheme 4. Intermolecular aminocarbonylation.

azaindolin-2-one derivatives. This reaction does not require any microwave or ultrasound and can be used for large scale synthesis using the conventional heating. Further studies with the synthesis of the C3 phenyl substituted indolin-2-one are in progress.

Acknowledgment

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Supplementary data

Supplementary data (experimental detail, reaction conditions and characterisation of products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.123.

References and notes

1. (a) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407; (b) Huber, K.; Schemies, J.; Uciechowska, U.; Wagner, J. M.; Rumpf, T.; Lewrick, F.; Suss, R.; Sippl, W.; Jung, M.; Bracher, F. *J. Med. Chem.* **2010**, *53*, 1383–1386; (c) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527–4547; (d) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9644; (e) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003–3025; (f) Volk, B.; Barkóczy, J.; Hegedus, E.; Udvari, S.; Gacsalyi, I.; Mezei, T.; Pallagi, K.; Kompagne, H.; Levay, G.; Egyed, A.; Harsing, L. G.; Spedding, M., Jr.; Simig, G. *J. Med. Chem.* **2008**, *51*, 2522–2532; (g) Sharma, V.; Kumar, P.; Pathak, D. *J. Het. Chem.* **2010**, *47*, 491–502.
2. Prakash, C. R.; Theivendren, P.; Raja, S. *Pharmacol. Pharm.* **2012**, *3*, 62–71.
3. (a) Sundberg, R. J. In *Indoles*; Academic Press: London, 1996; Vol. 17, p. 152; (b) Hardegger, E.; Corrodi, H. *Helv. Chim. Acta* **1956**, *39*, 514–517; (c) Cabri, W.; Candiani, I.; Colombo, M.; Franzoi, L.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 949–952; (d) Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Lett.* **1994**, *35*, 7673–7676; (e) Jones, K.; McCarthy, C. *Tetrahedron Lett.* **1989**, *30*, 2657–2660; (f) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron Lett.* **1988**, *29*, 6657–6660; (g) McAllister, L. A.; Turner, K. L.; Brand, S.; Stefaniak, M.; Procter, D. J. *J. Org. Chem.* **2006**, *71*, 6497–6507; (h) McAllister, L. A.; McCormick, R. A.; Brand, S.; Procter, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 452–455; (i) McAllister, L. A.; Brand, S.; Gentile, R. de.; Procter, D. J. *J. Chem. Commun.* **2003**, 2380–2381; (j) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256–4268; (k) Kuethe, J. T.; Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 7082–7083; (l) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017–1022.
4. Crestini, C.; Saladino, R. *Synth. Commun.* **1994**, *24*, 2835–2841.
5. (a) Ali, B. E.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc* **1996**, *118*, 4264–4270; (b) Hirao, K.; Morii, N.; Joh, T.; Takahashi, S. *Tetrahedron Lett.* **1995**, *36*, 6243–6246.
6. Arumugam, V.; Routledge, A.; Abell, C.; Balasubramanian, S. *Tetrahedron Lett.* **1997**, *38*, 6473–6476.
7. Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435–443.
8. Dandia, A.; Bhati, D. S.; Jain, A. K.; Sharma, G. N. *Ultrason. Sonochem.* **2011**, *18*, 1143–1147.
9. (a) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494–499; (b) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486–7500.
10. Rao, K. P.; Basak, A. K.; Raju, A.; Patil, V. S.; Reddy, L. K. *Tetrahedron Lett.* **2013**, *54*, 5510–5513.
11. See the Supporting information page S3–S5, for the synthetic procedure of tosylhydrazone.
12. The reported yield has been arrived after deducting the impurity appearing in NMR & LCMS.
13. *General experimental procedure*: To a screw cap vial was added tosylhydrazone (1.0 mmol) in 1, 4-dioxane (5 mL). Then charged tetraethylammonium bromide (1.0 mmol) followed by the addition of DBU (2.5 mmol) and Mo $(CO)_6$ (1.0 mmol) at room temperature. The mixture was heated to 110 °C for 1 h. The reaction progress was monitored by using TLC. After consumption of starting material the reaction mixture was filtered through celite bed and washed with ethyl acetate. The ethyl acetate layer was washed with water and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford crude compound. The crude compound was purified flash chromatography on Biotage instrument using 4.0 g snap cartridge and eluted with ethyl acetate in hexane to give indoline-2-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.45 (s, 1H), 6.81-6.79 (d, J = 8 Hz, 1H), 6.93–6.89 (t, J = 8 Hz, 1H), 7.20–7.13 (d, J = 8 Hz, 2H), 10.34 (br s, 1H).^{13}C NMR (100 MHz, DMSO-d_6) δ 35.7, 109.1, 121.1, 124.3, 125.7, 127.4, 143.6, 176.3. ES-MS (m/z): 134.2 (M^++H).